The World Journal of Biological Psychiatry

ISSN: 1562-2975 (Print) 1814-1412 (Online) Journal homepage: www.tandfonline.com/journals/iwbp20

World Federation of Societies of Biological Psychiatry (WFSBP) consensus statement on candidate biomarkers for anorexia nervosa

Hubertus Himmerich, Johanna Louise Keeler, Joseph A. King, Stefan Ehrlich, Lisa-Katrin Kaufmann, Cynthia M. Bulik, Sarah Cohen-Woods, Tracey Wade, Howard Steiger, Linda Booij, Palmiero Monteleone, Giammarco Cascino, Alessio Maria Monteleone, Ulrich Cuntz, Ulrich Voderholzer, Selamawit Alemayehu Tessema, Yael D. Lewis, Magnus Sjögren, Johannes Hebebrand, Jochen Seitz, Marta Tyszkiewicz-Nwafor, Olga Karpenko, Hiba Mutwalli, Sergueï O. Fetissov, Isabelle Mack, Namrata Dhopatkar, Sabrina Mörkl, Carol Kan, Maria M. Uribe, Kazuhiro Yoshiuchi, Nadine Abuobeid, Dimitrios Kapogiannis, Daniel Stein, Sevgi Bektas, Daniel J. Müller, Philip Gorwood, Philibert Duriez, Chloé Tezenas du Montcel, Elżbieta Paszyńska, Susan L. McElroy, Wiesława Dominika Wranik, Fernando Fernandez-Aranda, Philip S. Mehler, Hana Papežová, Radka Roubalová, Petra Procházková, Rebecca Morris, Piotr Lewczuk, Christoph Hiemke, Michael Berk, Andreas Karwautz, Janet Treasure, Siegfried Kasper, the WFSBP Task Force on Biological Markers & the WFSBP Task Force on Eating Disorders

To cite this article: Hubertus Himmerich, Johanna Louise Keeler, Joseph A. King, Stefan Ehrlich, Lisa-Katrin Kaufmann, Cynthia M. Bulik, Sarah Cohen-Woods, Tracey Wade, Howard Steiger, Linda Booij, Palmiero Monteleone, Giammarco Cascino, Alessio Maria Monteleone, Ulrich Cuntz, Ulrich Voderholzer, Selamawit Alemayehu Tessema, Yael D. Lewis, Magnus Sjögren, Johannes Hebebrand, Jochen Seitz, Marta Tyszkiewicz-Nwafor, Olga Karpenko, Hiba Mutwalli, Sergueï O. Fetissov, Isabelle Mack, Namrata Dhopatkar, Sabrina Mörkl, Carol Kan, Maria M. Uribe, Kazuhiro Yoshiuchi, Nadine Abuobeid, Dimitrios Kapogiannis, Daniel Stein, Sevgi Bektas, Daniel J. Müller, Philip Gorwood, Philibert Duriez, Chloé Tezenas du Montcel, Elżbieta Paszyńska, Susan L. McElroy, Wiesława Dominika Wranik, Fernando Fernandez-Aranda, Philip S. Mehler, Hana Papežová, Radka Roubalová, Petra Procházková, Rebecca Morris, Piotr Lewczuk, Christoph Hiemke, Michael Berk, Andreas Karwautz, Janet Treasure, Siegfried Kasper, the WFSBP Task Force on Biological Markers & the WFSBP Task Force on Eating Disorders (01 Mar 2026): World Federation of Societies of Biological Psychiatry (WFSBP) consensus statement on candidate biomarkers for anorexia nervosa, The World Journal of Biological Psychiatry, DOI: 10.1080/15622975.2026.2626934

To link to this article: https://doi.org/10.1080/15622975.2026.2626934

© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

View supplementary material

Published online: 01 Mar 2026.

Submit your article to this journal

Article views: 771

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=iwbp20

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
https://doi.org/10.1080/15622975.2026.2626934

REVIEW ARTICLE

OPEN ACCESS Check for updates

World Federation of Societies of Biological Psychiatry (WFSBP) consensus statement on candidate biomarkers for anorexia nervosa

Hubertus Himmerich[a,b], Johanna Louise Keeler[a], Joseph A. King[c], Stefan Ehrlich[c,d], Lisa-Katrin Kaufmann[e,f], Cynthia M. Bulik[g,h], Sarah Cohen-Woods[i], Tracey Wade[i], Howard Steiger[j,k], Linda Booij[j,k], Palmiero Monteleone[l], Giammarco Cascino[l], Alessio Maria Monteleone[m], Ulrich Cuntz[n,o], Ulrich Voderholzer[n,p], Selamawit Alemayehu Tessema[q], Yael D. Lewis[r,s], Magnus Sjögren[t], Johannes Hebebrand[u], Jochen Seitz[u], Marta Tyszkiewicz-Nwafor[v], Olga Karpenko[w], Hiba Mutwalli[a,x], Sergueï O. Fetissov[y], Isabelle Mack[z,aa], Namrata Dhopatkar[b], Sabrina Mörkl[ab], Carol Kan[a,ac], Maria M. Uribe[ad], Kazuhiro Yoshiuchi[ae], Nadine Abuobeid[a], Dimitrios Kapogiannis[af,ag], Daniel Stein[s,ah], Sevgi Bektas[a,ai], Daniel J. Müller[aj,ak], Philip Gorwood[al,am], Philibert Duriez[am], Chloé Tezenas du Montcel[al,am], Elżbieta Paszyńska[an], Susan L. McElroy[ao,ap], Wiesława Dominika Wranik[aq], Fernando Fernandez-Aranda[ar,as], Philip S. Mehler[at,au], Hana Papežová[av], Radka Roubalová[aw], Petra Procházková[aw], Rebecca Morris[a], Piotr Lewczuk[ax,ay], Christoph Hiemke[az,ba], Michael Berk[bb], Andreas Karwautz[bc], Janet Treasure[a,b] and Siegfried Kasper[bd], the WFSBP Task Force on Biological Markers[**] the WFSBP Task Force on Eating Disorders[***]

[a]Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, Centre for Research in Eating and Weight Disorders (CREW), London, UK; [b]South London and Maudsley NHS Foundation Trust, London, UK; [c]Translational Developmental Neuroscience Section, Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Dresden, Germany; [d]Eating Disorder Treatment and Research Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany; [e]Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, Netherlands; [f]Experimental Psychopathology and Psychotherapy, Department of Psychology, University of Zurich, Zurich, Switzerland; [g]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [h]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; [i]Flinders University Institute for Mental Health and Wellbeing, Flinders University, Adelaide, Australia; [j]Eating Disorders Continuum, Douglas Mental Health University Institute, Montreal, Canada; [k]Department of Psychiatry, McGill University, Montreal, Canada; [l]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy; [m]Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy; [n]Center for Psychosomatic Medicine, Schön Klinik Roseneck, Prien am Chiemsee, Germany; [o]Forschungsprogramm für Psychotherapieevaluation im Komplexen Therapiesetting, Paracelsus Medizinische Universität, Salzburg, Austria; [p]Department of Psychiatry and Psychotherapy, Ludwig Maximilians Universität, Munich, Germany; [q]Psychiatry Department, St Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia; [r]Hadarim Eating Disorders Unit, Shalvata Mental Health Center, Hod HaSharon, Israel; [s]Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [t]Institute for Clinical Science, Umeå University, Umeå, Sweden; [u]Department of Child and Adolescent Psychiatry, Psychotherapy, and Psychosomatics, and Center for Translational Neuro and Behavioural Sciences, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [v]Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland; [w]Mental-health Clinic No. 1 Named after N. A. Alexeev, Moscow, Russia; [x]Department of Clinical Nutrition, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; [y]Neuroendocrine, Endocrine and Germinal Differentiation and Communication Laboratory, University of Rouen Normandie, Rouen, France; [z]Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany; [aa]Centre of Excellence for Eating Disorders (KOMET), Tübingen, Germany; [ab]Department of Medical Psychology, Psychosomatics and Psychotherapy, Medical University of Graz, Graz, Austria; [ac]Vincent Square Eating Disorder Service, Central and North West London NHS Foundation Trust, UK; [ad]Universidad Nacional de Colombia, Bogota, Colombia; [ae]Department of Stress Sciences and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [af]National Institute on Aging, Baltimore, MD, USA; [ag]Department of Neurology, Johns Hopkins University, Baltimore, MD, USA; [ah]Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [ai]Department of Psychology, Hacettepe University, Ankara, Türkiye; [aj]Department of Psychiatry, University of Toronto, Toronto, Canada; [ak]Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital of

CONTACT Hubertus Himmerich hubertus.himmerich@kcl.ac.uk Centre for Research in Eating and Weight Disorders (CREW), Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

[**]Ana Andreazza (Canada), Bernhard Baune (Germany), Michael Berk (Australia), Brisa Fernandes (Australia), Carla Gallo (Peru), Manfred Gerlach (Germany), Christoph Hiemke (Germany), Marek Jarema (Poland), Dimitrios Kapogiannis (USA), Sidney Kennedy (Canada) Yong-Ku Kim (Korea), Piotr Lewczuk (Germany), Andrea Lopez Mato (Argentina), Peter Riederer (Germany), Mohamed Saoud (France), Martin Schalling (Sweden), Florence Thibaut (France), Marat Galievich Uzbekov (Russia), Lakshmi Yatham (Canada), Moussa B. H. Youdim (Israel).

[***]Ursula Bailer, (Germany), Sevgi Bektas (Türkiye), Cynthia M. Bulik (USA), Chiara Conti (Italy), Martina De Zwaan (Germany), Angela Favaro (Italy), Fernando Fernandez-Aranda (Spain), Serguei Fetissov (France), Anja Hilbert (Germany), Hubertus Himmerich (UK/Germany), Hans Hoek (Netherlands), Carol Kan (UK), Olga Karpenko (Russia), Andreas Karwautz (Austria), Siegfried Kasper (Austria), Walter H. Kaye (USA), Cheyenne Lee (Singapore), Yael D. Lewis (Israel), Susan L. McElroy (USA), James Mitchell (USA), Palmiero Monteleone (Italy), Sabrina Mörkl (Austria), Daniel J. Müller (Canada), Hiba Mutwalli (Saudi Arabia), Bruno P. Nazar (Brazil), Hana Papežová (Czech Republic), Jan M. Sjögren (Sweden), Howard Steiger (Canada), Daniel Stein (Israel), Christopher P. Szabo (South Africa), Marta Tyszkiewicz-Nwafor (Poland), Ulrich Voderholzer (Germany), María Mercedes Uribe Isaza (Colombia), Tracey Wade (Australia), Wiesława D. Wranik (Canada), See Heng Yim (Hong Kong, China), Kazuhiro Yoshiuchi (Japan).

Supplemental data for this article is available online at https://doi.org/10.1080/15622975.2026.2626934.

© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

Würzburg, Würzburg, Germany; [al]Institut de Psychiatrie et Neurosciences de Paris, Université Paris Cité, Paris, France; [am]GHU PARIS Psychiatrie & Neurosciences, Hôpital Sainte-Anne, Paris, France; [an]Department of Integrated Dentistry, Community Dentistry Section, Poznan University of Medical Sciences, Poznan, Poland; [ao]Lindner Center of HOPE, Mason, OH, USA; [ap]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [aq]Department of Community Health, and Epidemiology, Dalhousie University, Halifax, Canada; [ar]Department of Clinical Psychology, University Hospital of Bellvitge-IDIBELL and University of Barcelona, Barcelona, Spain; [as]CIBER Physiopathology of Obesity and Nutrition (CIBERobn), ISCIII, Barcelona, Spain; [at]ACUTE Center for Eating Disorders and Severe Malnutrition at Denver Health, Denver, CO, USA; [au]Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA; [av]Department of Psychiatry, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [aw]Institute of Microbiology of the Czech Academy of Sciences, Prague, Czech Republic; [ax]Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen and Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [ay]Department of Neurodegeneration Diagnostics, Medical University of Białystok, Białystok, Poland; [az]Department of Psychiatry and Psychotherapy, University Medical Center of Mainz, Mainz, Germany; [ba]Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center of Mainz, Mainz, Germany; [bb]Institute for Mental and Physical Health and Clinical Translation (IMPACT), Deakin University, Geelong, Australia; [bc]Eating Disorders Care & Research Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria; [bd]Center for Brain Research, Medical University of Vienna, Vienna, Austria

ABSTRACT

Objectives: This World Federation of Societies of Biological Psychiatry (WFSBP) consensus paper aims to summarise and evaluate the published study results on objectively measurable biological markers associated with anorexia nervosa (AN).

Methods: The relevant literature was reviewed by the WFSBP Task Forces on Eating Disorders and on Biological Markers, and a consensus regarding the significance of the published evidence was reached.

Results: Candidate biological markers that have been associated with AN include clinical (e.g. body weight), molecular (e.g. genetic, epigenetic, hormonal, immunological, metabolomic), cellular (e.g. leukocytes), neuroimaging (e.g. structure, function, connectivity), digital, cardiac and neurophysiological parameters. Some clinical and laboratory parameters are risk markers in clinical practice. Biological markers have pathophysiological relevance in understanding the biological and metabolic pathophysiology of AN and its physical health consequences. Few studies have examined pharmacogenetics or therapeutic drug monitoring as tools to monitor and guide the treatment of AN.

Conclusions: Biological markers will hopefully soon enable clinicians to intervene earlier in a more targeted manner to mitigate treatment resistance. However, the current scientific basis for most biological markers are group comparisons only. Studies on sensitivity, specificity and the prognostic value of these markers are lacking.

ARTICLE HISTORY
Received 10 October 2025
Revised 1 February 2026
Accepted 1 February 2026

KEYWORDS
Anorexia nervosa; biomarkers; genetics; epigenetics; neuroimaging; metabolomics; microbiome; digital markers

1. Introduction

Genetic findings have recently suggested reframing anorexia nervosa (AN) as a metabo-psychiatric disorder (Bulik, Carroll, et al. 2021). Further evidence of the significance of biological factors in the pathophysiology of AN has arisen from metabolic and endocrinological (Minor et al. 2009; Galusca et al. 2015; Duncan et al. 2017), immunological (Dalton et al. 2018; Escelsior et al. 2022), and neuroimaging (Seitz et al. 2016, 2018; Walton et al. 2022; Kaufmann et al. 2023) research. Examples of clinical indications for a strong contribution of biological factors are the female predominance of the disorder and the onset age between 10 and 15 years, the association with starvation and the strong correlation between premorbid body weight and weight loss (Keys et al. 1950; Hebebrand, Hildebrandt, et al. 2022; Hebebrand, Seitz, et al. 2024). AN can result in physical health consequences such as bradycardia, hypotension, hair loss, and endocrine dysregulation including amenorrhoea. These changes reflect starvation which is a key symptom of AN. Thus, there is an overlap between the physical and psychological symptoms of starvation (Keys et al. 1950) and the symptoms of AN (Hebebrand, Hildebrandt, et al. 2022). During starvation all tissues adapt to a reduced energy intake to enhance the probability of survival (Hebebrand, Hildebrandt, et al. 2022; Hebebrand, Plieger, et al. 2024). Those changes can entail reduced energy expenditure, the emergence of hyperactivity which may be interpreted as food foraging behaviour (Hebebrand, Hildebrandt, et al. 2022) and/or thermoregulatory adaptation (Gutierrez et al. 2024). Apart from the physical adaptation, profound psychological changes are associated with starvation, including preoccupation with food, altered eating behaviour, depression, insomnia and increased rigidity (Keys et al. 1950; Hebebrand, Hildebrandt, et al. 2022).

As the largest endocrine organ, the adipose tissue secretes hundreds of adipokines (Kershaw and Flier 2004; Lehr et al. 2012). Thus, loss of adipose tissue results in dysregulation of adipokine secretion, which in turn mediates the adaptation to starvation. The

hormone leptin figures prominently in this adaptation process. Hypoleptinaemia (absolute or adjusted for body weight) represents a core endocrine finding in AN, which underlies the neuroendocrine adaptation to starvation (Hebebrand, Hildebrandt, et al. 2022; Hebebrand, Plieger, et al. 2024).

Brain imaging in AN has consistently shown reductions in the volume of grey (GM) and white (WM) matter, as well as reduced connectivity between different brain areas (Seitz et al. 2016, 2018; Walton et al. 2022; Kaufmann et al. 2023). These changes may be the biological correlates of cognitive problems associated with AN, such as deficiencies of central coherence, cognitive flexibility, memory and visuospatial processing (Reville et al. 2016; Stedal et al. 2021; Keeler et al. 2022b). The underlying molecular changes of reduced brain matter appear to be a consequence of starvation potentially mediated by the downregulation of neurotrophic factors like leptin (Wronski et al. 2024, 2023a, 2023b) and brain-derived neurotrophic factor (BDNF) (Keeler et al. 2022c; Hebebrand, Plieger, et al. 2024). These alterations may be linked to decreased neuroplasticity and neuronal damage, suggested by research indicating increases in markers of neuronal injury such as neurofilament light chain (NfL) in AN (Nilsson et al. 2019; Hellerhoff et al. 2021). In addition to the molecular, cellular, tissue or organ signals, digital biomarkers have recently emerged, that aim to capture human behaviour and symptoms (Zierer et al. 2024).

Such structural, molecular or behavioural markers may be used as indicators for biological processes underlying the development of AN, the manifestation of its subtypes, its prognosis, or response to an intervention (FDA-NIH Biomarker Working Group 2016). These indicators might therefore have value as biomarkers for diagnosis, monitoring, pharmacodynamic/response, prediction, prognosis, safety, and susceptibility/risk. A single biomarker may qualify for more than one of these categories and one biomarker in isolation would likely be difficult to interpret due to interrelationships with other biomarkers (Califf 2018). Complicating this, biomarkers are not a unitary construct and encompass biomarkers of risk, diagnosis or trait, state, stage, response and prognosis (Davis et al. 2015).

To be used as biomarkers in psychiatry, these signals should be specifically associated with a mental disorder and should help to facilitate diagnosis and/or contribute to the determination of prognosis, risk or treatment efficacy (Charney et al. 2002). This leads to a very important issue in biomarker research, namely a clear definition of the Context of Use (COU) (Cummings et al. 2025). What is the role of a given biomarker: is it a diagnostic biomarker? Is it a prognostic biomarker? Is it a biomarker useful for differential diagnosis, or perhaps in screening? Alternatively, perhaps we expect it to predict therapy response or perhaps risk of disease recurrence? All these questions need to be critically addressed before evaluation of any biomarker in any medical condition, as they have consequences for decision whether to accept a candidate for routine application (in a given COU) or not (Cummings et al. 2025). For example, entirely different sensitivities and specificities are expected from biomarkers to be applied for diagnostic or screening purposes. In the context of AN, such biomarkers may be useful for future subtyping, assessing and/or predicting the development of the eating disorder (ED) or personality and behavioural traits, assessing cognitive and emotional capacity, and importantly, informing treatment decisions.

Technical innovations have made the exploration of novel biomarkers possible. These technological advances include epigenetics (Booij and Steiger 2020), metabolomics (Jia et al. 2023), the microbiome (Fan et al. 2023), and multiplex measurement of inflammatory biomarkers (Breithaupt et al. 2024). Additionally, some of the molecules that have been identified as altered in AN have been identified as potential drug targets. For example, several case reports on the use of metreleptin – a recombinant analogue of the human hormone leptin – in AN have been published with positive results (Milos et al. 2020; Gradl-Dietsch et al. 2023). The Task Force EDs of the World Federation of Societies of Biological Psychiatry (WFSBP) recognises the new technical opportunities, the increased understanding of the biological factors of AN and the novel conceptualisation of AN as a metabo-psychiatric disorder. It is also mindful of the plethora of newly discovered findings and the heterogeneity of the quality of published studies which makes guidance for clinicians and researchers desirable. This consensus paper on biomarkers in AN summarises published study results on molecular, electrophysiological, neuroimaging, digital and other objectively measurable markers that have been reported to be associated with AN, the health risks associated with AN, and the treatment of AN.

2. Methods

The WFSBP Task Force EDs reached consensus on the relevant biological markers that should be included in this consensus statement. The authors organised

themselves within workstreams that covered: genetics and epigenetics; neuroimaging; molecular markers of brain plasticity and damage; appetite regulators, gastrointestinal signalling molecules and adipokines; stress markers; sexual and social hormones; immunological markers; metabolomics; the microbiome and markers of the gut-brain axis; salivary markers; neurophysiological markers; digital biomarkers; physical health risk and refeeding markers; therapeutic drug monitoring and pharmacogenetics.

Each workstream decided on the specific search strategy for each biomarker depending on the available evidence. Literature searches included the databases PubMed, ISI Web of Science and PsycInfo, supplemented by hand-searches through the reference lists of included papers and relevant reviews. Individual searches were conducted per biomarker, with search terms relating to that biomarker in combination with 'anorexia nervosa'.

Identified meta-analyses were included in the results section. Evidence from lower-level research such as pilot, cross-sectional and longitudinal studies was also reported if necessary for the assessment of the biomarker in question or if no meta-analyses were published.

3. Results

3.1. Genetics and epigenetics

3.1.1. Genetic research in anorexia nervosa

The recognition that genetics play a role in EDs, and in behavioural conditions more broadly, has been said to be *'one of the most dramatic shifts in the modern history of the behavioural sciences'* (Plomin 2000). Indeed, the nature vs. nurture debate has moved on to a nature *and* nurture discourse, where researchers are determining the extent of contribution from both, and how nurture (environmental factors) may influence our nature (genetic predisposition), and in turn how our nature may predict nurture (such as dietary selection) (Dick et al. 2010).

Twin studies represent one of the most critical tools for elucidation of genetic and environmental factors in the development of mental health conditions. Simply put, twin studies are leveraged through the comparison of concordance rates between monozygotic (identical) twins – who share ~100% of their assorting alleles and dizygotic (non-identical) twins – who share ~50% of their assorting alleles. This enables researchers to establish the extent of genetic contribution to variance in the conditions observed. In EDs, twin-based heritability (h^2_{twin}) estimates demonstrate moderate to high genetic contributions to AN (28–88%), bulimia nervosa ([BN] 54–83%), binge eating disorder ([BED] 39–57%) (Thornton et al. 2011; Bulik et al. 2019) and avoidant restrictive food intake disorder ([ARFID] 79%) (Dinkler et al. 2023). With the establishment that genetic variation contributes to the risk of developing these conditions, there is a drive to elucidate the underlying molecular genetic aetiology of EDs – to identify specific genetic risk variants. We note, however, this does not preclude identifying environmental contributions, which will be addressed later in this section.

3.1.2. Risk genes: genome-wide association studies (GWAS)

In the 1990s and early 2000s, genetic studies used a candidate gene approach, which involves identifying an *a priori* hypothesised gene (or groups of genes) based commonly on the function of that gene and evaluating if genetic variation within that gene differs between those affected by an ED, and those not. These focused on monoaminergic, appetite, and weight-regulation systems (e.g. serotonin, leptin, ghrelin, fat mass and obesity-associated protein), and did not identify replicable genetic risk loci (positions of variation on the deoxyribonucleic acid [DNA]) (Pinheiro et al. 2010). Biotechnology and statistical genetic methods have progressed since this time, with the advent of genome-wide association studies (GWAS) (Loos 2020). GWAS allow researchers to interrogate millions of genetic markers across the entire genome, without relying on *a priori* assumed functions and mechanisms as was necessary in candidate gene studies.

While a paradigm-shifting biotechnological advancement, GWAS does come with its own challenges, one of the most widely recognised being the need for exceptionally large sample sizes of tens, or even hundreds of thousands of cases and controls (Wray et al. 2018). The genetic architecture of complex disorders such as AN, BN, BED, and ARFID mean that thousands of genetic variants each individually contribute an extremely small effect size to increase risk for developing these conditions (Fu et al. 2013). The issue of small effect sizes is then combined with the need for hundreds of thousands of statistical tests to analyse each genetic variant captured individually, in relation to the outcome of interest. This requires statistical correction to avoid false positives, meaning the standard threshold for significance ($p < 0.05$) must be substantially lower ($p < 5 \times 10^8$) to obtain robust and reliable results and to ensure that subsequent interrogation of identified loci are wise investments in effort and money.

To achieve such substantial numbers the Psychiatric Genetics Consortium (PGC) was created in 2007 establishing a global infrastructure for the investigation of the genetic architecture of multiple psychiatric disorders (Sullivan et al. 2018). In 2013, the ED working group was established, led by Cynthia Bulik, with an initial focus on AN. Through the determination and collaboration of hundreds of researchers worldwide, replicable genetic risk variants are now being identified for AN (Boraska et al. 2014; Duncan et al. 2017; Watson et al. 2019, 2022), and studies are underway identifying risk variants for binge-eating behaviour, BN, BED, and ARFID (Bulik, Thornton, et al. 2021; Bulik et al. 2023; Monssen et al. 2024).

The first GWAS meta-analysis was published in 2012 and investigated six ED related phenotypes: drive for thinness, body dissatisfaction, bulimia, weight fluctuation symptoms, breakfast skipping, and childhood obsessive-compulsive personality disorder trait (Boraska et al. 2012). This meta-analysis included three studies and in its largest analysis (weight fluctuation) included 2,976 individuals (807 cases and 2,169 healthy controls [HCs]). These analyses identified no genome-wide significant loci, reflecting the pattern seen regularly in psychiatric disorders where much larger sample sizes are required to identify robust replicable genetic loci. Following this, analyses have been mostly focused on AN and phenotypes within this condition.

The first global GWAS meta-analysis involved a collaborative effort between the genetic consortium for AN (GCAN) and the Wellcome Trust Case Control Consortium 3 (WTCCC3) in 2014, and identified no genome-wide significant associations with 17,767 individuals (2,907 cases and 14,860 HCs) (Boraska et al. 2014). As shown in Table 1 initial findings in meta-analyses proved inconsistent (further detail can be found in Table S1). In 2017, the PGC Eating Disorders Working Group (PGC-ED) carried forward the GCAN/WTCCC3 and combined them with genotypes from other samples collected globally to publish their first large-scale meta-analysis in AN (Freeze I). This meta-analysis identified a single genome-wide significant signal on chromosome 12q13.2 spanning six genes, with the top variant (rs4622308) being in high linkage disequilibrium (and thus closely associated) with already identified risk variants for type I diabetes, rheumatoid arthritis, and other autoimmune conditions (Duncan et al. 2017).

The second PGC-ED meta-analysis substantially increased numbers to include 16,992 AN cases and 55,525 HCs from 15 countries (Freeze II), and identified eight genome-wide significant loci, which highlighted potential roles of many brain-expressed genes (Watson et al. 2019) (see Table 1). The previously identified top 'hit' from the 2017 meta-analysis did not achieve genome-wide significance in this analysis but remained close to significance. Such fluctuation is not uncommon in early phases of genetic discovery as samples sizes remain low and variability in phenotyping across contributing samples exist. A further analysis was undertaken by the PGC-ED to investigate if early-onset AN (defined as onset prior to 13 years) and typical-onset AN present with differential genomic risk loci; with these analyses also limited by lower sample numbers (1,269 early-onset, 6,998 typical-onset, and 25,042 HCs) no early-onset AN loci were identified.

In addition to estimating heritability from twin studies, it is also possible to estimate single nucleotide polymorphism-based heritability (h^2_{SNP}) *via* GWAS. Single nucleotide polymorphisms (SNPs) are the genetic variants measured in a GWAS, and SNP-based heritability refers to the heritability that is captured within these studies at the molecular genetic level. Importantly, since GWAS only capture common genetic variation (and not rare variants), it is expected that h^2_{SNP} will be lower than h^2_{twin}. The h^2_{SNP} of AN reported in the aforementioned AN GWAS range from 0.17 to 0.25 (Duncan et al. 2017; Watson et al. 2019) and did not appear to differ markedly between early- and typical-onset AN (Watson et al. 2022).

While GWAS have firmly centred on AN, a recent meta-analysis was published investigating an approximate BED phenotype (Burstein et al. 2023). Allocation of caseness for BED was not based on clinical diagnoses. A supervised machine-learning (ML) method was applied in the Million Veterans Program cohort, which then underwent cross-ancestral GWAS ($n = 822$ cases). This analysis identified three genome-wide significant loci in three genes (*HFE, MCHR2, LRP11*), which did not overlap with AN risk loci identified to date; however, the findings are very early in the stage of BED molecular genetic risk identification and larger analyses with rigorous phenotyping will be required to ascertain the robustness of these loci.

In addition to the focus on AN, research has also centred on single nucleotide polymorphisms, a specific type of genetic variant characterised by the substitution of a single nucleotide (or base) in the DNA sequence. Copy number variation is another form of genetic variation which involves regions of DNA that are repeated, with the number of copies varying between individuals. Copy number variation can influence gene transcription and translation and has been associated with a range of complex diseases, including

Table 1. Summary table reporting genome-wide association meta-analyses of eating disorder phenotypes in reverse chronological order.

		Discovery stage			
Authors (year)	Condition	N	n (patients / controls)	Ancestry	Results: GWAS loci pathway/network analyses/functional characterisation PRS (variance captured)
Walker et al. (2025)	AN (Replication only)	2	12,458 Anorexia Nervosa Genetics Initiative (ANGI; 7,414/5,044) Replication in 387,190 UK Biobank (1,260/385,930)	European	**Pleiotropic loci** In 178 copy number variants reported to be pleiotropic in 54 complex and Mendelian traits/disorders no copy number variants reached significance following correction for multiple testing.
Burstein et al. (2023)	BED	2	362,712 (African GWAS $n = 77,574$; European GWAS $n = 285,138$)	African and European	**GWAS loci** Two genome-wide significant loci from European GWAS in *HFE* and near *MCHR2*. One further genome-wide significant locus in *LRP11* in cross-ancestral meta-analysis. **Pathway / Network analysis** In addition to neuropsychiatric, obesity-related, autoimmune, and cancer traits, enrichment was found in gene sets related to haem and uric acid metabolism. **PRS (variance captured)** European-ancestry PRS significantly predicted BED in two independent cohorts, but not in a third smaller cohort. Variance captured not reported. Also predicted UKBB iron overload and iron deficiency ($\beta = -0.03$; $p = 0.01$). **Functional characterisation** Phenome-wide association studies (PheWAS) of lead SNPs from GWAS implication in iron dysregulation, iron metabolism and iron deficiency anaemia disorders.
Watson et al. (2022)	AN (age of onset, early-onset and typical-onset)	13	AN age of onset: 13 cohorts 41,316 (9335/31,981); early-onset AN: 5 cohorts 26,311 (1269/25,042) typical-onset AN: 5 cohorts 32,040 (6998/25,042)	European	**GWAS loci** No genome-wide significant loci in GWAS of early-onset AN. Two genome-wide significant loci in GWAS of typical-onset AN (rs3821875, rs4641158). Heritability estimates (h^2_{SNP}) were 0.01–0.04 for AN age of onset, 0.16–0.25 for early-onset AN, and 0.17–0.25 for typical-onset AN. **PRS (variance captured)** PRS for age of onset explained 0.13% (liability scale R^2) of variance, for early-onset explained 0.85%, and for typical-onset 0.25% of the variance. **Functional characterisation** Gene expression was most enriched in brain tissues although not significant. Gene sets were also not significant.
Watson et al. (2019)	AN	33	72,517 (16,992/55,525)	European	**GWAS loci** Eight genome-wide significant loci located near genes *NCKIPSD*, *CADM1*, *ASB3/ERLEC1*, *MGMT*, *FOXP1*, *PTBP2*, *CDH10*, *NSUN3*. Genome-wide common variant heritability (h^2_{SNP}) was 0.11–0.17 (s.e.=0.01). **Pathway / Network analysis** Gene-wise analysis identified 79 significant genes (majority chromosome 3). A significant biological pathway linked to regulation of embryonic development. **Functional characterisation** Significant loci annotated to 121 brain-expressed genes; enrichment of genes highly expressed in brain (including cerebellum and neurons) and linked to feeding behaviours. **PRS (variance captured)** PRS explained ~1.7% of phenotypic variance (liability scale R^2)

(*Continued*)

Table 1. Continued.

Authors (year)	Condition	Discovery stage N	Discovery stage n (patients / controls)	Ancestry	Results: GWAS loci pathway/network analyses/functional characterisation PRS (variance captured)
Huckins et al. (2018)	AN *Replication:*	9 2	17,643 (2,158/15,485) *in silico* $n = 1,033/3,733$; *de novo* $n = 261/1,500$	European	No genome-wide significant associations.
Duncan et al. (2017)	AN	12	14,477 (3,495/10,982)	European	**GWAS loci** One genome-wide significant locus (12q13.2; top variant in region – rs4622308) Genome-wide common variant heritability (h^2_{SNP}) of AN was 0.20 (SE = 0.021). **Pathway / Network analysis** Multiple genes reached gene-based significance due to high LD in region, most located in region around top SNP (rs4622308). No pathways were significant. **Functional characterisation:** GTEx search did not identify any patterns of gene expression for top genes in region.
Boraska et al. (2014)	AN	15 15	17,767 (2,907/14,860) European 11,306 (2,677/8,629) Japanese 879 (458/421)	European European and Japanese	**GWAS loci** One genome-wide significant SNP (rs4957798) in the discovery meta-analysis, but not replicated in the global meta-analysis, with no genome-wide significant SNPs identified.
Boraska et al. (2012)	Six eating disorder phenotypes: DT, BD, WF, BS, OCPD, Bulimia	3	DT $n = 2,680$ BD $n = 2,789$ (821/1,968) WF $n = 2,976$ (807/2,169) BS $n = 2,967$ (798/2,169) OCPD $n = 2,773$ (761/2,012) Bulimia $n = 1,360$ (633/727)	European	No genome-wide significant associations.

Abbreviations: AN = Anorexia Nervosa; BED = Binge Eating Disorder; BD = body dissatisfaction; BS = breakfast skipping behaviour; CI = confidence interval; CNV = copy number variant; DT = Drive for Thinness; GWAS = Genome wide association studies; h^2_{SNP} = single nucleotide polymorphism-based heritability; LD = linkage disequilibrium; OCPD = Childhood Obsessive-Compulsive Personality Disorder trait; OR = odds ratio; PheWAS = Phenome-wide association studies; PRS = polygenic risk scores; SE = standard error; SNP = single nucleotide polymorphism; UKBB = UK Biobank; WF = weight fluctuation symptoms. *Detailed table available in Supplementary Materials (*Table S1*).*

psychiatric conditions (Mollon et al. 2023). To date, only one large-scale investigation of rare copy number variants has been published in EDs, and specifically AN (Walker et al. 2025), leveraging data from the Anorexia Nervosa Genetics Initiative (ANGI) and the UK Biobank. This study was limited due to differing genomic arrays used across cohorts and variation in cohort characteristics such as age and how diagnoses were established, requiring cautious interpretation of results. None of the 15 tested loci, including 16p11.2, NRXN1, 22q11.2 and 3q29 deletions, displayed significant associations with AN (Walker et al. 2025), even though the 3q29 deletion, for example, had previously been associated with several relevant conditions, including failure to thrive, mild to moderate intellectual disability (Yilmaz et al. 2017; Chang et al. 2019), feeding and weight gain problems (Wang et al. 2011), bipolar disorder (Sudmant et al. 2015), and schizophrenia (Cheng et al. 2005).

As demonstrated in Table 1, as sample size increases, power improves for these analyses. This work is ongoing through the PGC-ED and global collaboration of scientists. It is likely that larger meta-analyses will identify a greater number of variants, as has been the pattern of discovery in other psychiatric disorders. Through further identification, biological networks and pathways implicated in AN will be uncovered and improve our understanding of how genetic and biological factors influence AN risk and potentially inform the development of biologically informed pharmacotherapeutics. Though current understanding of the genetic aetiology of BN, BED, and ARFID is more limited, large global efforts are underway to advance understanding of both genetic and environmental risk for all EDs.

3.1.3. Genetic correlations

GWAS also enable the calculation of genetic correlations (SNP-r_g) across disorders or traits using summary statistics (Bulik-Sullivan et al. 2015). SNP-r_g reveal the extent to which two traits are influenced by the same genetic factors and can be positive (the same genetic factors influence both traits in the same direction; e.g. either increasing or decreasing risk for both traits) or negative (the same genetic factors influence both traits but in opposite directions; e.g. increasing risk for

one trait while decreasing risk for the other). Genetic correlations can inform the underlying genetic aetiology of disorders and can be highly informative with respect to shared mechanisms underlying disorders. We did not conduct a systematic review of the vast genetic correlation literature, but rather briefly summarise the over-arching findings. A more detailed review can be found in Watson et al. (2023).

Unsurprisingly, AN has strong positive genetic correlations with other psychiatric disorders and traits (SNP-r_g = 0.17 − 0.49) including obsessive-compulsive disorder, depression, anxiety, and schizophrenia. Less anticipated are the significant genetic correlations between AN and a range of metabolic, anthropometric, and glycaemic traits (SNP-r_g = −0.22 to −0.32). Negative genetic correlations are observed between an array of anthropometric traits such as body mass index (BMI), obesity and waist to hip ratio and metabolic traits such as fasting insulin, insulin resistance, leptin, and type 2 diabetes, with the single positive genetic correlation being with high-density lipoprotein (HDL) cholesterol (Duncan et al. 2017; Watson et al. 2019). Adjusting for BMI did not significantly alter correlations with non-BMI traits, indicating that these correlations are not driven by genetic influences for BMI. The interpretation of these results is that some of the same genetic factors that increase risk for AN, decrease risk for developing traits such as obesity and type 2 diabetes. Furthermore, these results encourage the consideration of both psychiatric and metabolic/anthropometric factors in understanding the biology of AN. Sample sizes are still too small to determine whether the same patterns hold for early and typical onset AN or across genders. However, an initial glimpse into differences across EDs suggest that while AN, BN, and BED show similar genetic correlations with psychiatric traits, they diverge markedly on anthropometric and metabolic traits, with the two binge-type EDs showing positive (and not negative) genetic correlations with metabolic and anthropometric phenotypes (Hübel et al. 2021).

3.1.4. Polygenic risk scores

GWAS also enable the calculation of a metric called a polygenic risk score (PRS) also known as polygenic score or genetic risk score. A PRS captures the magnitude of the genetic load an individual carries for a particular disease or trait by creating a weighted sum of all known risk alleles that an individual carries (Figure 1) (Wray et al. 2021). The purple curve represents a theoretical PRS distribution for individuals with AN and the green curve represents the PRS

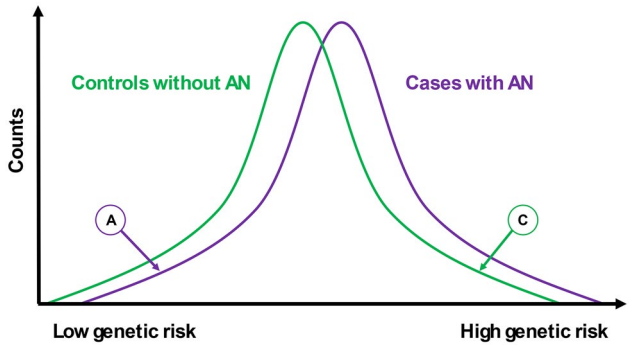

Figure 1. Theoretical distribution of a polygenic risk score for anorexia nervosa. AN = anorexia nervosa. Graph A depicts the counts of cases with AN, graph C of controls without AN.

distribution for HCs (i.e. individuals without AN). Although in general, individuals with AN have higher PRS for the disease than HCs, the curves overlap considerably. The individual demarcated by the purple circle 'A' represents an individual with AN who has a relatively low polygenic risk for AN, whereas the person depicted by the circle marked C is someone with high genetic risk, who has nonetheless never developed the illness. This drawing clearly illustrates why PRS cannot be utilised as a genetic test for AN or other studied traits. There are many individuals with a high AN PRS who never develop the illness as well as many individuals with low polygenic risk who do develop AN (Bulik 2024). The huge overlap of such curves representing the small differences between distributions are a general problem in biomarker research that causes false positivity or false negativity.

Importantly, the robustness of a PRS for any illness depends on the genetic architecture of the target trait as well as the size of the GWAS from which it is derived. Larger samples of heritable traits yield more robust PRS and confidence in the ability of PRS to index disease risk. As stated unequivocally by Wray et al. (2021) 'PRS are not and never will be stand-alone predictors of common diseases'.

Of the 16 identified studies that investigated AN PRS and ED phenotypes, 12 analysed clinical diagnoses as the outcome (AN or ARFID), while four investigated ED symptoms, three in the same cohort (Avon Longitudinal Study of Parents and Children; ALSPAC) and one a global disordered eating outcome in addition to disordered eating behaviours such as purging, binging, and restriction ((Curtis et al. 2024); see Table S2). Overall, it is evident that AN PRS is associated relatively consistently with AN diagnosis, with one study reporting no relationship with ARFID (Koomar et al. 2021). This is the first and currently only study

correlating AN PRS with a clinical ED outside of AN, but it represents a well-powered study for PRS analyses in terms of the target sample size ($n > 3{,}000$ cases) and therefore suggests that different genetic drivers may contribute to these two pathologies. It is important, however, to further explore the relationship of AN PRS with other ED phenotypes such as BED, BN, and other specified feeding and eating disorders (OSFED) especially atypical AN (AAN) as there is evidence that AN PRS predicts a measure of global disordered eating, and symptoms and behaviours of EDs, in adolescents in the general population (Curtis et al. 2024; Herle et al. 2021; Yilmaz et al. 2023) and not just clinical diagnoses. PRSs could also be improved in the future to be more specific for different sub-types or phenotypes within clinical diagnoses as evidenced by distinct PRSs generated for early and later ages of onset for AN (Watson et al. 2022). There is some indication that the current AN PRS may be more highly associated with outcomes in females (Papini et al. 2024; Yilmaz et al. 2023), and may also interact with other AN risk factors such as maternal genitourinary tract infection, age at birth, method of delivery, parental education, income, and psychiatric history (Papini et al. 2024).

In addition to AN, many other psychological and psychiatric phenotypes have been correlated with AN PRS. Of these many reported no significant effects with psychiatric disorders such as major depressive disorder, bipolar disorder, panic disorder, attention deficit hyperactivity disorder, alcohol dependence or suicidal behaviours. However, a few studies did report positive associations with suicide related behaviours such as suicide attempts and non-suicidal self-injury, and cannabis use disorder (Table S3). Relationships that were reported were nominal in effect size, and suggest that while AN PRS may influence some other psychological or psychiatric traits these appear small or context dependent, for example with gender differences observed in neuroticism where AN PRS was a predictor only in men (Gale et al. 2016).

These conflicting findings may in part be driven by the relatively early nature of PRS investigations in AN relative to some other psychiatric disorders. As previously described, the discovery cohort determines the power of the PRS as a tool to predict outcomes: at this stage, AN PRS studies are relatively small and so the PRSs derived on these discovery cohorts may still have relatively low power. Over time, as the discovery cohort increases, the field can further explore relationships between AN PRS and other psychological and psychiatric outcomes with greater certainty. At this stage relationships appear to be weak, and inconsistent outside of AN diagnosis and ED phenotypes themselves.

Similarly inconsistent effects are reported across the few studies that investigated a range of brain structure and function where sex-specific relationships are reported (e.g. (Leehr et al. 2019)) or no associations identified at all (e.g. (Taquet et al. 2021)). Studies have also investigated reproductive timing (Ni et al. 2019) with evidence for a relationship, and inflammatory bowel disease or other medical conditions with no evidence (Table S4). Finally, AN PRS has been associated with urbanicity, nutrient intake, academic performance, and other established risk factors for AN.

More consistent findings, like the relationship between AN PRS and AN diagnosis, are observed with metabolic phenotypes (Table S5). Most of these studies indicate higher AN PRS is associated with lower, or slower growth, and reduced body mass indicators such as weight, BMI, bone mineral density, and weight trajectory. In line with some observations in other phenotypes, there is some evidence that these effects are limited to or more pronounced in females (see Table S5).

Overall, AN PRS appears to predict AN diagnosis, some ED symptoms, metabolic phenotypes, and some established risk factors for AN. There is also some evidence that these relationships may be particularly evident in women or girls. It is too early to be certain what the relationship is between AN PRS and the multiple other phenotypes that have been explored, in part likely due to the restricted power of our current AN PRS tool. The observation that effects may be more pronounced, or restricted to, women or girls may also be driven by the fact that the discovery cohorts upon which the PRS has been trained upon possess a majority of female cases with only ~3% male cases with AN (Watson et al. 2022). This may restrict the applicability of the AN PRS based on the current GWAS discovery cohorts to populations including males.

In addition to the limited number of men with AN included in the original discovery GWAS, it is notable that most studies used European-ancestry cohorts. Critically this is the case for the discovery GWAS and so generalisability of the PRS may not be transferable across ancestries. To date, target cohorts have also been predominantly European ancestry and so we do not know how the present AN PRS may perform in other ancestry populations.

We have focused on how AN PRS may correlate with a range of phenotypes and outcomes. Other PRSs have also been correlated with AN as the outcome, for example the PRS for BMI. While this is outside the scope of this review, it is worth noting that the

strongest PRS predictors beyond the AN PRS for AN are those for metabolic traits such as BMI (Hübel et al. 2021). The mechanism for this relationship is not yet clear with some evidence that this may be due to differences in BMI predicting ED risk, rather than the biological drivers for BMI also driving ED risk (Watson et al. 2019); but this remains a highly active area of research. As mentioned above when discussing genetic correlations, while there is evidence for genetic correlations across EDs and other psychiatric traits, there appears to be marked differences on genetic correlations across EDs with anthropometric and metabolic traits, with the two EDs defined by binge eating (BN and BED) showing positive genetic correlations with metabolic and anthropometric phenotypes – the opposite to that seen with restrictive EDs (Hübel et al. 2021).

3.1.5. Epigenetics

Epigenetic mechanisms influence gene expression (and corresponding phenotypic variations) through molecular modifications that regulate gene activity in the absence of physical changes to the DNA code (Li 2021). Epigenetic changes, mainly involving DNA methylation, histone modifications and noncoding ribonucleic acid ([RNAs] (Peixoto et al. 2020), appear to occur in an environmentally responsive and site-specific fashion – meaning that, through epigenetic programming, environmental exposures occurring throughout the life span can influence phenotypic manifestations by enabling or silencing the expression of specific genetic tendencies (e.g. (Szyf 2015)). Consequently, with respect to many physical- and mental-illness phenotypes, epigenetic effects have the potential to influence the progression (depending upon an individual's life history) from genetic susceptibility to full-blown illness and back (Recillas-Targa 2022; Steiger et al. 2023). Data have implicated epigenetic processes in diverse medical and psychiatric problems – including EDs (see (Booij and Steiger 2020; Campbell et al. 2011; Hübel et al. 2021; Steiger and Booij 2020)).

3.1.5.1. DNA methylation. DNA methylation, the best-studied of epigenetic mechanisms, involves the addition of methyl groups to DNA sites at which a cytosine is followed by a guanine – called CpGs. DNA methylation acts in a site-specific fashion, so as to selectively block or suppress the expression of specific genes (Fujita et al. 1999; Inamdar et al. 1991). Diverse environmental factors influence the methylation of DNA: Prenatal influences, acting through maternal placental signalling or paternal epigenetic marks in sperm, have been documented (Chan et al. 2018), as have various effects associated with perinatal, childhood and adulthood exposures to stress (Steiger and Booij 2020; Steiger and Thaler 2016). In addition, because certain micronutrients (e.g. folate, choline, betaine, methionine) participate in methyl-transfer reactions upon which DNA methylation depends (Anderson et al. 2012), nutritional factors also have an influence (Guarasci et al. 2018; Koklesova et al. 2021). Given the preceding, DNA methylation constitutes a potential 'platform' upon which effects of heredity, nutritional status and life experiences (during perinatal, developmental and later-life phases) converge. DNA methylation may therefore have intriguing potentials as a biomarker for a disorder in which life stresses and nutritional triggers are so obviously implicated (Steiger and Booij 2020).

The literature on DNA methylation in EDs includes three non-systematic reviews (Booij and Steiger 2020; Hirtz and Hinney 2020; Steiger and Booij 2020), one systematic review of the literature on AN, BN and BED up to 2017 (Hübel, Marzi, et al. 2019), and another covering the literature on AN up to 2023 (Käver et al. 2024). We conducted an updated literature search on May 5, 2025 using Pubmed, Google Scholar and Web of Science literature databases and identified no relevant additional papers that had not been treated in the previous reviews cited. Given the preceding, rather than providing a systematic review here, we instead summarise findings that indicate replicable methylation changes at specific genes in participants with AN. Interested readers are referred to the previous reviews cited above for comprehensive treatments.

3.1.5.2. Methylation at candidate genes. Like candidate-gene studies in the field of psychiatric genetics, candidate-gene studies on DNA methylation in AN have produced unstable results. Käver et al. (2024) reviewed findings (available up to 2023) from 17 systematically selected case-control studies targeting candidate-gene methylation in AN. In short, these studies inconsistently pointed to altered methylation of genes involved in neurotransmitter function, neural plasticity, social attachment, and appetite and energy regulation – including genes regulating dopamine, serotonin, oxytocin, BDNF, leptin, ghrelin, among others.

3.1.5.3. Epigenome-wide association studies. There are five published reports, conducted by three different research groups, documenting results of epigenome-wide methylation studies (EWAS) in people with AN – all using Illumina platforms to assay DNA obtained from whole blood or leukocytes (Booij et al. 2015; Iranzo-Tatay et al. 2022; Kesselmeier et al. 2018; Steiger et al. 2019; Steiger et al. 2023) (see Table 2). Broadly,

Table 2. Summary of the methodology and findings of the five EWAS studies in individuals with anorexia nervosa.

Study	Booij et al. (2015)	Kesselmeier et al. (2018)	Steiger et al. (2019)	Iranzo-Tatay et al. (2022)	Steiger et al. (2023)
Sample	All females 29 active AN 15 NED	All females 47 active AN 47 NED, lean 100 NED, population-based 5 MZ pairs discordant for active-AN	All females 75 active AN, 31 in stable remission 41 NED	All females 7 MZ twin pairs discordant for active AN 7 active AN (singletons) 7 NED (singletons)	All females 145 active AN 49 in remission [3] 1 year 64 NED
Cell type	Leukocytes	Whole blood	Leukocytes	Whole blood	Leukocytes
DNA methylation method	Infinium Human Methylation 450 BeadChip Kit	Infinium Human Methylation 450 BeadChip Kit	Infinium Human Methylation 450 BeadChip Kit / Infinium MethylationEPIC 850 BeadChip Kit [1]	Infinium MethylationEPIC 850 BeadChip Kit	Infinium Human Methylation 450 BeadChip Kit / Infinium MethylationEPIC 850 BeadChip Kit[1]
# CGs	AN *vs.* NED: 14 probes $q<.05$	An *vs.* lean NED: 51 CGs AN *vs.* population-based NED: 81 CGs. All based on 2 different reference free methods, $p<.01$ MZ sample: 26/51 CGs and 54/81 CGs were in same direction as results from the AN *vs.* lean *vs.* population NED comparisons, all $p> .01$	AN *vs.* NED: 58 CGs; AN *vs.* remitted: 265 CGs; remitted *vs.* NED: 0 CGs. All $q<.01$	MZ twin with AN vs. healthy co-twin: 9 CGs ($q<.05$). 6 CGs were replicated in a AN vs NED comparison (singletons) ($p<.05$)	AN *vs.* NED: 205 CGs; AN *vs.* remitted: 162 CGs; remitted *vs.* NED: 0 CGs. All $q<.01$
Genes identified as being differentially methylated in AN in 2 or more EWAS studies					
NR1H3	X	X	X		X
TNXB	X	X	X		
SYNJ2			X	X	X
PRDM16	X	X			
HDAC4	X	X			

Abbreviations: AN = anorexia nervosa; MZ = monozygotic; NED = no eating disorder.[1] Only CGs common to both the 450 BeadChip Kit and the Infinium Methylation EPIC 850K BeadChip Kit were analysed.

comparisons across individuals with active AN or those who never had an ED reveal differential methylation at multiple CpG sites. The number of identified CpGs varied across studies, with studies with larger samples reporting larger numbers of significant probes. Across studies, DNA methylation levels were reported to be altered at CpG sites mapping primarily onto genes involved with mental, metabolic and immune functions.

To date, there have been no meta-analyses on findings from EWAS studies in AN – and we feel it premature to attempt to do so given that the available studies implicate heterogeneous methods, and that three out of the five studies in AN, involve overlapping samples and are published by the same group. This being the case, rather than a systematic review, we conducted a qualitative analysis of findings from the five available EWAS studies in AN aimed at identifying reproducible epigenetic biomarkers. For these comparisons, we applied two criteria: To qualify as a possible biomarker, an identified gene (irrespective of the CpG site) had to have been found to be (i) differentially methylated in at least two EWAS studies conducted by independent research groups, or (ii) differentially methylated in at least one EWAS study and, as well, associated with AN at genome-wide significance in at least one of the available case-control GWAS studies on AN. Stringent application of the preceding criteria isolated five genes of interest: *NR1H3*, *TNXB*, *SYNJ2*, *PRDM16* and *HDAC4* (see Table S6).

NR1H3 was found to be differentially methylated in AN in four of the five EWAS studies, three conducted by one group (Booij et al. 2015; Steiger et al. 2019; Steiger et al. 2023) and one by another (Kesselmeier et al. 2018). *NR1H3 is* involved in lipid metabolism, energy homeostasis, and inflammation. Three EWAS studies conducted by two different research groups found hypermethylation at the *TNXB* gene (Booij et al. 2015; Kesselmeier et al. 2018; Steiger et al. 2019). Involved in connective tissue formation, *TNXB* has been implicated in the development of syndromes characterised by hyperflexibility (like Ehlers-Danlos) that have also been linked to AN (Baeza-Velasco 2021). Three EWAS studies from two independent groups found differential methylation at the *SYNJ2* gene (Iranzo-Tatay et al. 2022; Steiger et al. 2019; Steiger et al. 2023), which is responsible for nerve-cell communications. In addition, the *PRDM16* gene, associated with thermogenesis, was associated with AN in two independent studies (Booij et al. 2015; Kesselmeier

et al. 2018). The same two EWAS studies reported altered methylation levels at the *HDAC4* gene, which regulates histone deacetylation.

Applying our second criterion for establishing epigenetic biomarkers, we compared results from the five available EWASs to findings published in eight GWAS studies comparing individuals with AN to those with no ED (Wang et al. 2011; Nakabayashi et al. 2009; Wade et al. 2013a; Boraska et al. 2014; Duncan et al. 2017; Li et al. 2017; Huckins et al. 2018; Watson et al. 2019). Interestingly, none of the genes previously associated with AN in GWASs (whether at genome-wide significance or as 'top hits') showed differential methylation levels in an EWAS study. We speculate that the latter tendency may differentiate pleiotropic genes for AN that, because they do not depend upon environmental factors, are strong candidates for direct genome-wide association (in GWASs) from genes whose phenotypic manifestations depend greatly upon epistatic (gene-environment) effects that are isolated in EWASs.

Some EWAS results have associated illness duration and lower BMI with more pronounced DNA methylation alterations, and disease remission (as indicated by full or partial weight restoration) with normalisation of methylation levels (see (Booij et al. 2015; Steiger et al. 2019; Steiger et al. 2023)) – as would suggest reversible alterations that correspond to illness activity and severity. The preceding implies that methylation levels have potential as markers of disease staging or therapeutic response.

3.2. Neuroimaging

3.2.1. Structural neuroimaging

Neuroimaging encompasses a set of methods utilised to investigate the structure and function of the brain. Over the last 30 years, a variety of neuroimaging methods have been used to study the brains of individuals with AN and help better understand the underlying biological mechanisms of the condition (King et al. 2018). This section provides a selective update on structural neuroimaging in AN, highlighting the most significant recent findings, challenges to scientific progress, and promising avenues for future research.

Modern non-invasive magnetic resonance imaging (MRI) techniques, including diffusion tensor imaging (DTI) and network-based approaches, have driven a recent surge in research on brain structure in AN. These efforts have resulted in several comprehensive meta-analyses and dedicated review articles (Barona et al. 2019; Bracké et al. 2023; Gaudio et al. 2019; Kappou et al. 2021; King et al. 2018; Meneguzzo et al. 2019; Monzon et al. 2017; Seitz et al. 2016; Su et al. 2021; Walton et al. 2022), as well as the establishment of an international consortium aimed at advancing our understanding of structural brain changes in EDs including AN (https://enigma.ini.usc.edu/ongoing/enigma-eating-disorders/).

The most applied structural neuroimaging method in AN research involves analysis of T1-weighted MRI brain scans, which allows for assessment of various macrostructural features of the brain by distinguishing between GM – primarily consisting of neuronal cell bodies, dendrites, and axon terminals – and WM, which comprises myelinated axonal pathways linking different brain regions. While most studies in AN samples have used voxel-based morphometry to investigate cortical and/or subcortical GM volume (Seitz et al. 2016; Su et al. 2021), there is an increasing trend towards surface-based approaches, which separate GM volume into its underlying components: cortical thickness and surface area (King et al. 2018). In recent years, a few studies in individuals with AN have begun exploring other metrics such as subcortical shape, cortical complexity and gyrification, (Bernardoni et al. 2018; Collantoni et al. 2020; Collantoni et al. 2025; Leppanen et al. 2019) conducting fine-grained analysis of subcortical substructures.

In acutely underweight individuals with AN, reductions in brain mass and enlarged ventricles are often readily visible in raw MRI scans and numerous case-control studies using the above methods have reported widespread reductions in GM in both adolescents and adult patients with AN relative to HCs (King et al. 2018). Recent mega- and meta-analyses in the largest samples to date indicate that the magnitude of GM reduction observed in AN in cortical thickness, subcortical volume and, to a lesser extent, surface area surpasses structural changes observed in any other psychiatric disorders (Bahnsen et al. 2022; Walton et al. 2022). Importantly, however, these deficits are closely linked to nutritional status and are significantly less pronounced after partial weight restoration (at least in younger patients with a shorter duration of illness (Kaufmann et al. 2020) and may not be detectable after long-term weight recovery. Together, the available data indicate that macrostructural GM alterations in AN may be a largely reversible consequence of underweight rather than a trait biomarker. However, the underlying cellular mechanisms remain unclear. There is also preliminary evidence that leptin levels are associated with structural alterations in specific brain areas (Wronski et al. 2025).

The integration of peripheral biomarkers into the analysis of dynamic brain structural alterations in AN, combined with the application of advanced multimodal methods – such as approaches rooted in artificial intelligence – promises new insight that may eventually help enhance clinical decision-making (Arold et al. 2023; Doose et al. 2023; Keeler et al. 2024).

In contrast to the amount of research focused on GM alterations in AN, relatively few studies have reported regional and/or global measures of WM volume. Similar to the findings in GM discussed above, meta-analytic data suggest that reduced WM volume in acutely underweight individuals with AN might be reversible following weight restoration (Seitz et al. 2016). However, more recent studies found no alterations in WM volume in AN relative to HCs (Geisler et al. 2022). Thus, the effect size of WM volume reduction in AN is likely to be considerably smaller than that of GM (Walton et al. 2022).

Research utilising DTI has provided more detailed insights into WM microstructure and connectivity in individuals with EDs (Barona et al. 2019; Gaudio et al. 2019; Zhang et al. 2020). DTI allows for the assessment of WM tract microstructural integrity by measuring water diffusivity along axons. Many studies investigating WM microstructure in AN have focused on group differences in diffusion strength at the voxel or tract level. In acutely underweight individuals with AN, several studies have reported altered WM matter microstructure, with evidence for both decreased and increased WM integrity (e.g. fractional anisotropy) in key tracts such as interhemispheric connections and limbic association fibres including the cingulum, corpus callosum, and fornix, as well as the superior longitudinal fasciculus and thalamo-cortical tracts (Barona et al. 2019; King et al. 2018). However, most studies did not address potential biases arising from partial volume effects (Kaufmann et al. 2017) and more research in larger (longitudinal) samples is needed to better understand dynamic changes in WM microstructure and connectivity in the disorder (Lloyd 2022).

A limited number of studies have utilised WM fibre tractography methods to assess structural connectivity in AN, yielding mixed results (Gaudio et al. 2019). While most of these studies have focused on specific tracts or connectivity from selected regions of interest, a few recent studies with robust statistical power have applied network-based graph-theoretic techniques to model whole-brain structural architecture. In a large sample of acutely underweight individuals with AN, Geisler et al. (2022) observed significant alterations in the WM connectome, including increased fractional anisotropy and reduced radial diffusivity, particularly in occipitoparietal regions. Similarly, a recent study in an even larger sample of acutely ill patients with AN by Lloyd et al. (2023) found reduced structural connectivity in subcortical networks and enhanced cortical network connectivity when compared to HCs. Collectively, these studies suggest that individuals with AN may have disruptions in the structural connections between brain regions.

3.2.2. Functional connectivity

Intrinsic neural activation and intrinsic functional connectivity describe spontaneous neural activity and functional interactions between brain regions while a person is at rest, without external tasks or stimuli (Van Den Heuvel and Pol 2010). These measures are assessed using functional MRI (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and arterial spin labelling (ASL). Intrinsic functional connectivity can be assessed at both global (across the whole brain) and local levels (for single brain regions), using network connectivity measures to evaluate the overall connection strength or to identify altered long- and short-range connections (Jiang and Zuo 2016; Van Den Heuvel and Pol 2010). Graph-theoretical measures further characterise the brain's network topology and organisational properties (Rubinov and Sporns 2010). Interindividual variation in intrinsic functional connectivity has been shown to allow individual identification with 78-95% accuracy and holds high predictive value for behavioural outcomes, such as cognitive performance (Mansour L et al. 2021). This section offers a focused overview of functional neuroimaging in AN, summarising recent advances and key findings across the acute phase, weight-related changes, and long-term recovery.

In the acute stage of AN, intrinsic neural activation has been examined in a meta-analysis comparing individuals with AN and HCs, revealing reductions in activity in the anterior and middle cingulate cortex, alongside increases in activity in the right parahippocampal gyrus (Su et al. 2021). While meta-analyses investigating intrinsic connectivity are currently lacking, a systematic review suggests overlapping alterations across studies within corticolimbic regions (Gaudio et al. 2016), with mixed directionality. Whole-brain analyses of long-range connections consistently report wide-spread weakened functional connectivity (Ehrlich et al. 2015; Kaufmann et al. 2023; Lotter et al. 2021; Sudo et al. 2024) and altered network topology (Geisler et al. 2016; Kaufmann et al. 2023) in the acute stage of AN. Additionally, some studies report elevated connectivity in regions such as

the dorsolateral prefrontal cortex (Steward et al. 2022; Sudo et al. 2024) and the striatum (Membrives et al. 2021; Muratore et al. 2024; Uniacke et al. 2019; Via et al. 2021). However, it should be noted that there is considerable heterogeneity across studies in terms of connectivity measures and brain networks examined.

Weight-related changes in intrinsic connectivity have been investigated in isolated longitudinal studies, with mixed findings. Increased long-range connectivity has been found to normalise during weight restoration (Cha et al. 2016; Uniacke et al. 2019; Via et al. 2021). However, analyses of weakened long-range connectivity suggest only partial normalisation (Kaufmann et al. 2023; Lotter et al. 2021), with persistent reductions in connectivity between regions of salience, fronto-parietal, and visual brain networks (Kaufmann et al. 2023; Uniacke et al. 2019). The degree of recovery may vary depending on patient characteristics, such as age (i.e. younger individuals may recover more quickly), and the specific connectivity measures analysed (i.e. short-range connections may recover more rapidly) (Seidel et al. 2024).

Among long-term weight-recovered individuals with AN, evidence remains mixed. Some studies report reduced connectivity in fronto-parietal, visual, and auditory networks (Boehm et al. 2016; Favaro et al. 2012; Scaife et al. 2017), while others describe increased connectivity in the default mode network (Cowdrey et al. 2014) or no residual alterations (Lotter et al. 2021), compared to HCs. Notably though, even in cases where no differences in network connectivity were detected, long-term recovered individuals could still be distinguished from HCs with high accuracy (>70%) based on intrinsic functional connectivity patterns (Geisler et al. 2020), suggesting a persistent aberrant brain network configuration in these individuals.

Overall, in the acute stage of AN, both intrinsic neural activity and functional connectivity appear to be weakened. Alterations in fronto-parietal and visual networks likely persist after weight restoration, potentially serving as trait markers of AN. These findings are consistent with evidence linking weaker intrinsic connectivity to more severe ED symptoms in healthy (self-reported absence of neurological or psychiatric disorders; no use of psychoactive medications; no other chronic diseases) young adults (Chen, Gao, et al. 2021), suggesting that disrupted intrinsic brain function may reflect a stable neurobiological marker of AN.

Table 3 shows the direction of change of all alterations of biological markers associated with AN in cross-sectional studies and with the changes of these markers with weight recovery.

3.3. Molecular markers of brain plasticity and damage

Neuronal biomarkers, encompassing entities like BDNF, tau, NfL, and synaptic biomarkers, have garnered significant attention due to their potential as indicators of neuronal damage, dysfunction, and plasticity alterations in neuropsychiatric disorders, including AN.

3.3.1. Brain-derived neurotrophic factor and other neurotrophins

BDNF is a growth factor within the neurotrophin family, which also includes neurotrophin (NT)-3, −4 and −5. It is found both in brain and peripheral nervous system and can be quantified in humans peripherally in the serum and plasma, as well as in cerebral spinal fluid, usually using an enzyme-linked immunosorbent assay (ELISA). Peripheral levels of BDNF are often used as a proxy of central BDNF levels, given that BDNF is able to cross the blood-brain barrier bidirectionally, and that the two have been found to be associated (Klein et al. 2011; Sartorius et al. 2009). The precursor form of BDNF (proBDNF) is proteolytically cleaved into a mature form (mBDNF); however both forms are biologically-active molecules that act on different pathways (Koshimizu et al. 2010). BDNF binds to two types of receptor, producing downstream effects on synaptic plasticity (*via* the tropomyosin receptor kinase B [TrkB] receptor) and apoptosis (*via* the p75 neurotrophin receptor) (Podyma et al. 2021). BDNF promotes neuronal survival and growth and differentiation of both neurons and synapses within the central and peripheral nervous systems (Kowiański et al. 2018; Tolwani et al. 2004). In brain, BDNF has important roles in the hippocampus, hypothalamus, ventral tegmental area, cerebellum and cerebral cortex (Miranda et al. 2019). It is also expressed in other organ systems (e.g. kidneys, retina and heart) and peripheral tissues (e.g. skeletal muscle and adipose tissue) (Afsar and Afsar 2022; Kimura et al. 2016; Matthews et al. 2009; Pius-Sadowska and Machaliński 2017). BDNF synthesis is markedly increased by physical exercise, which is thought to at least partially mediate exercise-induced synaptic plasticity and hippocampal neurogenesis (Liu and Nusslock 2018; Loprinzi and Frith 2019). Additionally, BDNF expression in the hippocampus has been found to be induced by leptin (Li et al. 2021), see section 3.6.1. for a detailed overview of leptin.

Three meta-analyses have investigated differences in peripheral concentrations of BDNF between people with AN and HCs (Brandys et al. 2011; Keeler et al. 2022c; Shobeiri et al. 2022). All found moderate-large

Table 3. Biological markers in anorexia nervosa. For genetic and epigenetic markers see Tables 1–2 and S1–S5, for clinical risk markers see table 4, and for digital markers table 5.

		AN vs. Controls			Before vs. after weight recovery				
Biological system	**Biological marker**	**Method and/or specimen**	**Alteration**	**Highest evidence**	**Method and/ or specimen**	**Change**	**Highest evidence**	**Relevance and comments**	**Further information, references: See section**
Neuroimaging Markers									
Brain	GM changes: Cortical volume, thickness and surface area Subcortical volume	MRI; head	↓	Meta-analyses	MRI; head	↑	Meta-analyses	Linked to nutritional status. Largely reversible after weight recovery.	3.2.1.
	WM changes Microstructural integrity Structural connectivity	MRI; head	↓↑ (microstructural integrity) ↓↑ (structural connectivity)	Cross-sectional studies	MRI; head	↑↓	Longitudinal studies	WM structural integrity is reduced. Connectivity findings are inconclusive and do not only show reduced connectivity. Longitudinal studies show partial normalisation.	3.2.1.
	Functional connectivity Long-range connectivity Short-range connectivity	MRI; head	↓	Systematic reviews	MRI; head	↑	Longitudinal studies	Partially linked to nutritional status. Quicker recovery in younger people. Slower recovery of long-range connectivity.	3.2.2.
Molecular markers of brain plasticity and damage									
Brain	BDNF	Plasma/Serum	↓	Meta-analyses	Plasma/Serum	↑	Meta-analysis	Consistently reported decreased BDNF serum concentrations in patients with AN in comparison to HC. Recovery to normal or potentially supranormal concentrations after weight restoration. State marker of AN. Not yet evaluated for clinical practice.	3.3.1.
	Tau protein	Serum	↑	Cross-sectional studies	Plasma/Serum	↓ after full weight recovery	Longitudinal studies	Maintains the stability of microtubules in axons. Elevated levels can indicate neuronal damage.	3.3.2.
	NfL	Serum	↑	Meta-analysis	Plasma/Serum	↓ after partial and full weight recovery	Longitudinal studies	NfL is released into surrounding fluid when neurons are damaged.	3.3.3.
	GFAP	Serum	↑	Cross-sectional studies	Serum	↓ after partial and full weight recovery	Longitudinal studies	Higher GFAP levels indicate astrocytic activation (astrogliosis) potentially because of brain damage.	3.3.4.

(*Continued*)

Table 3. Continued.

		AN vs. Controls			Before vs. after weight recovery				
Biological system	**Biological marker**	**Method and/or specimen**	**Alteration**	**Highest evidence**	**Method and/ or specimen**	**Change**	**Highest evidence**	**Relevance and comments**	**Further information, references: See section**
Signalling molecules associated with the regulation of appetite and metabolism									
Hypothalamic signalling molecules									
Hypothalamus	NPY	Plasma, serum, CSF	↑↓	Cross-sectional studies	CSF	No change after short-term weight restoration	Cross-sectional studies	Inconsistent in serum/plasma. ↑ NPY in CSF. Leptin inhibits NPY release.	3.4.1.
	α-MSH	Plasma/serum	↑↓	Cross-sectional studies	Serum	↑ with weight recovery	Longitudinal study	Serum α-MSH correlates negatively with BMI-SDS in HCs but not in AN Leptin stimulates α-MSH release,	3.4.2.
	NPB	Serum	↑	Cross-sectional studies	Serum	↓ with weight recovery	Longitudinal study	Ligand of GPR7/8. Elevated in acute AN. Decreases with refeeding. Only two small studies available.	3.4.3.
	NPW	Serum	↔	Cross-sectional studies	Serum	↔	Longitudinal study	Ligand of GPR7/8; no differences in AN. Unchanged with refeeding Only two small studies available.	3.4.3.
	KISS	Serum	↔	Longitudinal study	Serum	↔	Longitudinal study	No significant difference between acutely ill inpatients with AN, partial weight normalisation or control group	3.4.4.
	SPX	Serum	↓	Cross-sectional study	Serum	↔	Longitudinal study	Sigificantly lower in both acutely ill AN inpatients vs HC and after partial weight normalisation vs control No change of SPX during weight normalisation.	3.4.5.
	PNX	Serum	↓	Longitudinal study	Serum	↑	Longitudinal study	Significantly. lower in acutely ill AN inpatients than HCs Significantly lower in acutely ill AN inpatients than after partial weight normalisation	3.4.6.
	Orexin	Plasma	↓↑	Cross-sectional studies	Plasma	↑	Longitudinal study	Energy levels and psychological state influence orexin levels. Orexin levels seem to normalise with weight recovery.	3.4.7.

(*Continued*)

Table 3. Continued.

Biological system	Biological marker	AN vs. Controls: Method and/or specimen	AN vs. Controls: Alteration	AN vs. Controls: Highest evidence	Before vs. after weight recovery: Method and/or specimen	Before vs. after weight recovery: Change	Before vs. after weight recovery: Highest evidence	Relevance and comments	Further information, references: See section
Gastrointestinal signalling molecules									
GI tract	Total ghrelin	Plasma	↑	Meta-analysis	Plasma	↓	Meta-analysis	Ghrelin levels influenced by food intake, type of food and hydration level	3.5.1.
	Acyl-ghrelin	Plasma	↑	Meta-analysis	Plasma	↔	Meta-analysis	Acyl-ghrelin is the active form of ghrelin	3.5.1.
	Desacyl-ghrelin	Plasma	↑	Meta-analysis	Plasma	↓ after partial and full weight recovery	Longitudinal study	Desacyl-ghrelin is a form of ghrelin that lacks the acyl modification on its serine residue.	3.5.1.
	LEAP-2	Plasma	(↑) comparison with refed patients with AN, not HCs. ↓ following starvation in animals and humans	Longitudinal study; no cross-sectional comparison with HCs	Plasma	↓ after weight recovery	Longitudinal study	Patients with AN display higher LEAP-2 levels in undernourished compared to their refed state Abnormal LEAP-2 regulation during refeeding is associated with unstable remission	3.5.2.
	GLP-1	Plasma	↑↓	Cross-sectional studies	Plasma	↑ after 2 weeks of refeeding	Longitudinal study	Cross-sectional studies in AN inconsistent.	3.5.3.
	Cholecystokinin	Plasma	↑	Cross-sectional studies	N/A	N/A	N/A	In response to meals, especially those high in fat and protein content, cholecystokinin levels increase.	3.5.4.
	PYY	Serum	↑↓	Cross-sectional studies	Serum	↓↔	Longitudinal studies	PYY reduces food intake. Findings inconsistent in AN. PYY concentrations have been found to either decrease or remain unchanged during nutritional rehabilitation	3.5.5.
Signalling molecules of the adipose tissue									
Fatty tissue	Leptin	Plasma/Serum	↓	Meta-analysis	Plasma/Serum	↑	Longitudinal studies	Leptin reflects the amount of adipose tissue. Leptin is influences hypothalamic appetite regulators (α-MSH. NPY, AgRP) Leptin stiumulates the HPA, HPT and HPG axis.	3.6.1.
	Adiponectin	Plasma/Serum	↑	Meta-analysis	Plasma/Serum	↔	Longitudinal studies	IGF-1, GH, insulin and leptin influence adiponectin levels.	3.6.2.
	Resistin	Serum	↓	Meta-analysis	N/A	N/A	N/A		3.6.3.
	Vaspin	Serum	↑	Meta-analysis	Serum	↓	Longitudinal studies		3.6.4.
	Omentin	Serum	↑	Meta-analysis	Serum	Inconsistent	Longitudinal study		3.6.5.
	Visfatin	Serum and saliva	(↓)	Meta-analysis	Serum	Inconsistent	Longitudinal studies	Body fat content influences visfatin levels.	3.6.6.
	Obestatin	Serum	↑	Cross-sectional studies	Serum	↓	Longitudinal studies		3.6.7.
	Apelin	Plasma/Serum	↑	Cross-sectional studies	Plasma/Serum	↓	Longitudinal studies		3.6.8.

(*Continued*)

Table 3. Continued.

		AN vs. Controls			Before vs. after weight recovery				
Biological system	**Biological marker**	**Method and/or specimen**	**Alteration**	**Highest evidence**	**Method and/ or specimen**	**Change**	**Highest evidence**	**Relevance and comments**	**Further information, references: See section**
Stress-related hormones									
Hypothalamus	CRH	CSF	↑	Cross-sectional studies	CSF	Normalise after body weight gain	One longitudinal study	Stimulates the release of ACTH from the pituitary gland.	3.7.1.
Pituitary gland	ACTH	Plasma/Serum	↑	Meta-analysis	Plasma/serum	Inconsistent	Cross-sectional studies	Produced by the pituitary gland and stimulates the adrenal glands to produce cortisol.	3.7.1.
Adrenal gland cortex	Cortisol	Plasma/Serum	↑	Meta-analyses	Plasma/serum	Normalise after body weight gain	Longitudinal studies	State-dependent phenomenon likely due to the effects of starvation or undernutrition.	3.7.2
		Saliva during morning hours:	↑	Meta-analyses	Saliva	Normalise after body weight gain	Cross sectional studies		3.7.2.
		Urine	↑	Meta-analyses	N/A	N/A	N/A		3.7.2.
Sexual and social hormones									
Hypothalamus	GnRH	Plasma/Serum	↓	Cross-sectional studies	↑	Normalises with weight recovery	Longitudinal studies	Stimulates LH and FSH production.	3.8.1.
Pituitary gland	LH	Plasma/Serum	↓	Cross-sectional studies	↑	Normalises with weight recovery	Longitudinal studies	In females, triggers ovulation and the production of oestrogen and progesterone. In males, stimulates the testes to produce testosterone.	3.8.1.
Pituitary gland	FSH	Plasma/Serum	↓	Cross-sectional studies	↑	Normalises with weight recovery	Longitudinal studies	Stimulates the ovaries to produce eggs and oestrogen (females) and the testes to produce sperms (males).	3.8.1.
Adrenal gland	DHEA	Serum	↔	Meta-analyses	N/A	N/A	N/A	Produced by the adrenal gland, helps production of testosterone and oestrogen.	3.8.2.
Adrenal gland	DHEA-S	Serum	↓	Meta-analyses	N/A	N/A	N/A		3.8.2.
♀: Ovaries, adipose tissue ♂: Testes, adipose tissue	Oestradiol	Plasma/Serum	↓	Cross-sectional studies	↑	Normalises with weight recovery	Longitudinal studies		3.8.3.
♀: Ovaries, adipose tissue ♂: Testes, adipose tissue	Testosterone	Serum	↓	Meta-analysis	↑	Normalise with weight recovery	Longitudinal studies		3.8.3.
Hypothalamus	Oxytocin	Plasma/Serum/ CSF	↓	Meta-analysis	Serum/CSF	Inconsistent	Longitudinal studies	An opposite trend with higher (↑) oxytocin levels reported in a sample of adolescents with AN.	3.8.4.
Immunological markers									
Cytokines									
Blood	TNF-α	Plasma/Serum	↑ ↔	Meta-analyses	Plasma/Serum	↔	Meta-analysis		3.9.1.
	IL-1β	Plasma/Serum	↑ ↔	Meta-analyses	Plasma/Serum	↔	Meta-analysis		3.9.1.
	IL-6	Plasma/Serum	↑	Meta-analyses	Plasma/Serum	↓	Meta-analysis		3.9.1.
	IL-7	Plasma/Serum	↓	Meta-analyses	Plasma/Serum	↑	Meta-analysis		3.9.1.
	IL-15	Plasma/Serum	↑	Meta-analyses	Plasma/Serum	↔	Meta-analysis		3.9.1.

(*Continued*)

Table 3. Continued.

Biological system	Biological marker	AN vs. Controls: Method and/or specimen	AN vs. Controls: Alteration	AN vs. Controls: Highest evidence	Before vs. after weight recovery: Method and/or specimen	Before vs. after weight recovery: Change	Before vs. after weight recovery: Highest evidence	Relevance and comments	Further information, references: See section
Immunoglobulins									
Blood	α-MSH IgG antibodies	Plasma/serum	↓ levels but ↑ biological signalling efficiency of α-MSH in acute stage	Cross-sectional	Serum	↑ levels with weight recovery	Longitudinal in adolescents	Correlate negatively with BMI-SDS in both HCs and AN, ↑ affinity enhances carrier role of IgG for α-MSH	3.9.2.
	Ghrelin IgG antibodies	Plasma	↓ levels and affinity	Cross-sectional	Plasma	↑ levels with weight recovery	Longitudinal	↓ affinity reduces carrier role of IgG for ghrelin	3.9.2.
Saliva	sIgA	Saliva	↑	Cross-sectional studies	N/A	N/A	N/A		3.12.2.
Immune cells									
Blood, bone marrow	Leukocytes	Blood	↓	Meta-analysis	Blood	↑	Meta-analysis		3.9.3.
	Lymphocytes	Blood	↓	Meta-analyses	Blood	↑	Longitudinal studies		3.9.3.
	Eosinophils	Blood	↓	Meta-analysis	Blood	↑	Longitudinal studies		3.9.3.
	Basophils	Blood	↓	Meta-analysis	Blood	↑	Longitudinal studies		3.9.3.
	Monocytes	Blood	↓	Meta-analysis	Blood	↑90% IBW	Longitudinal studies		3.9.3.
	Neutrophils	Blood	↓	Meta-analysis	Blood	↑	Longitudinal studies		3.9.3.
Acute-phase protein									
Blood, liver	CRP	Plasma/Serum	↓	Meta-analyses	N/A	N/A	N/A		3.9.4.
Metabolomic markers									
Blood	Triglycerides	Plasma/Serum	↑	Meta-analysis	Plasma	↑	Longitudinal study	Triglycerides higher in AN relative to HCs.	3.10.3.
	Total cholesterol	Plasma/Serum	↑	Meta-analysis	Plasma/serum	↓	Meta-analysis	Increased cholesterol levels in AN are a result of HPA axis activation and low T3 levels.	3.10.3
	VLDL	Plasma/serum	↑	Cross-sectional studies	Plasma/serum	↑	Naturalistic longitudinal study	Increased VLDL in acute AN relative to HC. VLDL levels remain high despite weight recovery.	3.10.3
	LDL	Plasma/serum	↑	Meta-analysis	Plasma/serum	↔	Meta-analysis	Increased in AN relative to HC. Higher LDL in partially weight restored patients with AN compared to HC.	3.10.3
	HDL	Plasma/serum	↑	Meta-analysis	Plasma/serum	↔	Meta-analysis	Increased HDL at 7 years associated with a higher risk of developing AN HDL higher in AN relative to HCs.	3.10.3

(*Continued*)

Table 3. Continued.

		AN vs. Controls			Before vs. after weight recovery				
Biological system	**Biological marker**	**Method and/or specimen**	**Alteration**	**Highest evidence**	**Method and/ or specimen**	**Change**	**Highest evidence**	**Relevance and comments**	**Further information, references: See section**
Microbiome markers									
Faeces	Alpha diversity – Richness	Faeces	↔↑↓	Cross-sectional studies	Faeces	↔↑↓	Longitudinal studies		3.11.
	Alpha diversity – Diversity	Faeces	↔↑↓	Meta-analysis	Faeces	↔	Longitudinal studies		3.11
	Community Structure	Faeces	↑↓	Meta-analysis	Faeces	↔↑↓	Longitudinal studies	Direction of differences inconsistent.	3.11
	Taxa differences	Faeces	↑↓	Meta-analysis	Faeces	↔	Longitudinal studies	Tendencies towards ↓ butyrate-producing species and ↑ mucin-degrading species.	3.11
Salivary markers									
	α-Amylase	Saliva	↔	Meta-analysis	N/A	N/A	N/A	Nominally but not significantly higher α-amylase levels in AN compared to HC.	3.12.2.1.
	Opiorphin	Saliva	↔	Cross-sectional studies	N/A	N/A	N/A		3.12.2.4.
Neurophysiological markers									
Eye movements	Square wave jerks	Oculography	↑	Cross-sectional studies	N/A	N/A	N/A		3.13.1.

Abbreviations: α-MSH = alpha-melanocyte stimulating hormone; ACTH = adrenocorticotrophic hormone; AN = anorexia nervosa; BDNF = brain derived neurotrophic factor; BMI-SDS = body mass index standard deviation score; CRH = corticotropin releasing hormone; CRP = C-reactive protein; CSF = cerebrospinal fluid; DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulphate; FSH = follicle-stimulating hormone; GFAP = glial fibrillary acidic protein; GH = growth hormone; GLP-1 = glucagon-like peptide 1; GM = grey matter; GnRH = gonadotropin-releasing hormone; HC = healthy controls; HDL = high density lipoprotein; HPA = hypothalamus pituitary adrenal; HPT = hypothalamus pituitary thyroid; HPG = hypothalamus-pituitary-gonadal; IGF-1 = insulin-like growth factor 1; IgG = immunoglobulin G; IL = Interleukin; KISS = kisspeptin; LDL = low density lipoprotein; LEAP-2 = liver expressed antimicrobial peptide 2; LH = luteinising hormone; MRI = magnetic resonance imaging; N/A = not assessed or not applicable; NfL = neurofilament light chain; NPB = neuropeptide b; NPW = neuropeptide w; NPY = neuropeptide y; PNX = phoenixin; PYY = Peptide YY; sIgA = salivary immunoglobulin A; SPX = spexin; T3 = triiodothyronine; TNF-α = tumour necrosis factor-alpha; VLDL = very low density lipoprotein; WM = white matter;↑ = significantly higher values or increase, ↓ = significantly lower values or decrease, ↑↓ = inconsistent results, ↔ no significant change.

state-related reductions in BDNF during the acute stage of AN. Over the course of weight restoration, increases in BDNF have been found, with trends towards supranormal levels following longer-term weight restoration (Keeler et al. 2022c). This has been confirmed in the largest longitudinal study to date on adolescent patients with AN, which demonstrated that BDNF levels increased continuously during recovery and reached supranormal levels at 2.5-year follow-up (Borsdorf et al. 2021). These findings provide stronger evidence that elevated BDNF may be a risk factor for relapse given its anorexigenic effects. Subgroup analyses revealed that BDNF was lower only in the restricting subtype of AN (AN-R), and not the binge-purging subtype (AN-BP) (Keeler et al. 2022c). Additionally, it is possible that the reduction in BDNF may only exist in adults; whilst there were insufficient studies to perform subgroup analyses by age category in the aforementioned meta-analysis (Keeler et al. 2022c), other studies have failed to find state-related reductions in BDNF in adolescent populations (e.g. (Steinhäuser et al. 2021)). In terms of genetic risk for impairments in BDNF synthesis, a meta-analysis examining the Val66Met polymorphism (rs6265) of the BDNF gene found no greater association in people with AN than HCs (Brandys et al. 2013). However, recent reviews have provided more nuanced perspectives on this polymorphism's role in AN susceptibility, prognosis, and treatment response (Cao et al. 2024). Current evidence suggests the Val66Met polymorphism may interact with stress-related events and metabolic disturbances in modulating AN risk, representing a more complex relationship than previously understood.

BDNF is most likely to represent a state marker of AN, at least in AN-R, which is thought to be indicative of nutritional status rather than merely low weight (Keeler et al. 2022c). It has been suggested that reductions in BDNF may be a physiological adaptation to increase food intake, since BDNF has anorexigenic appetite-suppressing effects (Brandys et al. 2011). However, there has been some debate in the discussion of BDNF as a biomarker for AN, as whilst it demonstrates association with the illness and test-retest reliability, it may not have high enough specificity to distinguish AN from other forms of psychopathology (Brandys et al. 2011). For example, meta-analytic results suggest decreased BDNF in major depressive disorder (MDD), across most studies (Brunoni et al. 2008). It is possible that decreases in BDNF may represent a biomarker for general psychopathological processes, such as alterations in neuroplasticity, which may be present transdiagnostically. However, it should be noted that although treatment with antidepressants normalises BDNF levels in people with MDD (Brunoni et al. 2008), traditional antidepressants are largely ineffective in AN. Furthermore, Keeler et al. (2022c) found that AN-BP does not show decreases in BDNF despite presumably still having comorbid depressive features. There is mixed evidence for an association between depression symptoms and BDNF in people with AN (Mercader et al. 2007; Nakazato et al. 2009; Steinhäuser et al. 2021; Keeler et al. 2022a). Further investigations are necessary in order to ascertain whether reductions in BDNF may meet the criteria for classification as a biomarker of nutritional status or neuroplasticity for AN during the acute stages, which may in future aid clinicians to offer personalised BDNF-promoting treatments (e.g. ketamine, psilocybin; (Keeler, Kan, et al. 2024; Keeler et al. 2021)).

Additional neurotrophins of interest include vascular endothelial growth factor (VEGF), crucial for vasculogenesis and angiogenesis, glial cell-derived neurotrophic factor (GDNF), which promotes neuronal survival, and neurotrophin (NT)-3 and −4, both of which support the development of sensory neurons. A systematic review found that peripheral concentrations of VEGF-A and NT-4 were decreased in AN relative to HCs, with no differences in NT-3 or GDNF, although evidence is preliminary (Keeler et al. 2022c).

3.3.2. Tau protein

Tau is a microtubule-associated protein predominantly expressed in neurons of the CNS, playing a crucial role in stabilising microtubules and thereby influencing axonal transport and neuronal plasticity (Barbier et al. 2019; Mandelkow and Mandelkow 2012). Structurally, tau is an intrinsically disordered protein, because it lacks a stable structure and exists in a relatively unfolded state, allowing it to interact with various cellular components and adopt multiple conformations (Barbier et al. 2019; Michalicova et al. 2020; Mueller et al. 2021). Its function is finely regulated by post-translational modifications, notably phosphorylation, which modulates its affinity for microtubules and other interacting partners (Barbier et al. 2019; Mandelkow and Mandelkow 2012). Alterations in tau, such as hyperphosphorylation and aggregation, are hallmark features of several neurodegenerative diseases, including Alzheimer's disease (AD), where they form neurofibrillary tangles contributing to neuronal dysfunction and cell death (Barbier et al. 2019; Mandelkow and Mandelkow 2012).

Neurodegeneration processes can be detected and quantified using various biomarkers in cerebrospinal fluid (CSF) and blood, of which total tau is a non-specific biomarker, making it a very useful

screening tool and has been routinely used for decades in diagnostics of AD and prion diseases (Lewczuk et al. 2018b). In contrast, hyperphosphorylated Tau (p-tau) isoforms (like p-tau181 or p-tau217), seem to be more specific for AD, obviously reflecting AD-specific processes.

Recent advancements have enabled the measurement of specific tau species, such as p-tau and tau fragments (Gonzalez-Ortiz et al. 2023a, 2023b; Horie et al. 2023). These biomarkers offer insights into the disease stage, neuroprogression, and response to therapy (Gonzalez-Ortiz et al. 2023a, 2023b; Horie et al. 2023). For instance, CSF levels of p-tau181 and p-tau217 have been associated with amyloid pathology and tau PET measures, suggesting their utility in diagnosing AD and distinguishing it from other tauopathies (Gonzalez-Ortiz et al. 2023b). Moreover, novel blood-based biomarkers, such as plasma p-tau181, have shown promise in reflecting CNS tau pathology, potentially serving as accessible and cost-effective tools for early diagnosis and monitoring of disease progression (Gonzalez-Ortiz et al. 2023a).

Recent research has highlighted the relevance of tau in psychiatric conditions, including EDs. Elevated levels of tau have been observed in plasma of both patients with AN and those recovered from AN (Doose et al. 2022), suggesting potential neuronal injury or degeneration in this disorder. A longitudinal study found increased tau protein in acutely underweight patients with AN compared to HC participants but no changes in tau protein levels upon short-term partial weight restoration (Hellerhoff et al. 2021). This finding contrasts with the normalisation of other neuronal damage markers like NfL and glial fibrillary acidic protein (GFAP) after weight gain, suggesting persistent neuronal damage processes specifically in thin non-myelinated axons of cortical interneurons, where tau is abundantly found.

Recent research has further elucidated the relationship between tau protein levels and structural brain changes in AN. Unlike NfL, which shows significant associations with cortical thickness in several brain regions, tau protein levels do not demonstrate such direct relationships with cortical thinning (Doose et al. 2022). This differential pattern suggests that various neuronal damage markers in AN might reflect distinct pathophysiological processes affecting different neuronal populations and brain structures. The persistent elevation of tau protein despite weight restoration warrants further investigation into its long-term implications for cognitive function and recovery in AN.

3.3.3. Neurofilament proteins

Neurofilaments are cytoskeletal components predominantly expressed in long myelinated axons that are released into the CSF and peripheral blood in response to pathological processes involving axonal integrity (Bavato et al. 2024). Changes in neurofilament levels can be detected even in the presence of subclinical damage such as asymptomatic strokes or WM hyperintensities linked to silent cerebrovascular disease (Lewczuk et al. 2018a; Bavato et al. 2024; Rabl et al. 2024). Over the past years, research studies have assessed blood concentrations of NfL, the smallest and most abundant neurofilament subunit, in different clinical conditions (Barro et al. 2020; Rosengren et al. 1999; Sjögren et al. 2001). Promising findings in inflammatory, neurodegenerative, traumatic, and cerebrovascular diseases suggest a clinical application of NfL as a non-specific, all-around tool to assess the extent of brain damage (Barro et al. 2020). NfL measures in neurological conditions may allow for early pathological process detection, quantification of active brain pathology, monitoring treatment response, and predicting clinical outcome. On the other hand, NfL seems to be strongly influenced by age, which is a limiting factor when it comes to its routine application (age-related reference ranges will be probably needed).

There is growing evidence on NfL in AN, with multiple studies consistently demonstrating elevated plasma/serum concentrations, indicating ongoing neuronal injury and disruptions in axonal integrity. Nilsson et al. (2019) provided the first clear evidence of increased plasma NfL levels in AN compared to both HCs and recovered individuals with AN, with levels negatively associated with BMI. Across studies, despite some variability, results suggest that neurofilament levels are generally elevated in AN patients compared to HCs. The study by Nilsson et al. (2019) showed the largest effect size, while a study by Wentz et al. (2021) showed the smallest effect size. Hellerhoff et al. (2021) demonstrated that elevated NfL levels in acutely underweight AN patients decrease with weight restoration, and another study found no damage to neurons in individuals recovered from AN (Doose et al. 2022). These findings suggest that neuronal damage processes may partially normalise with nutritional rehabilitation, which aligns with imaging studies showing reversibility of certain brain changes after weight gain. In contrast to these results, one study investigated the relation to age and found increased NFL levels with age in people with AN and recovered from AN (AN-rec) implying that a permanent brain damage is induced by the disorder (Nilsson et al. 2019). This

was also corroborated by findings in a follow-up study in middle aged women that had suffered from AN (Wentz et al. 2021). Overall, the findings indicate that AN may be associated with increased neuronal injury, as reflected by elevated neurofilament levels. However, these are still findings that needs to be validated in follow-up studies and therefore must be interpreted with caution.

Recent research has established important neuroanatomical correlations with NfL levels in AN. Hellerhoff et al. (2023) found that higher baseline levels of NfL were significantly associated with lower cortical thickness in several brain regions, with the most prominent clusters located in bilateral temporal lobes. Importantly, this association was specific to AN and not detected in HCs, providing the first evidence linking a serum marker of axonal damage directly to structural brain alterations in AN. Links between NfL and structural brain changes had already been reported in neurodegenerative diseases such as Parkinson's and AD (Khalil et al. 2024).

3.3.4. Glial fibrillary acidic protein

GFAP is a type III intermediate filament protein that plays a crucial role in the cytoskeleton structure of glial cells and supports neighbouring neurons and the blood-brain barrier (BBB) (de Reus et al. 2024). GFAP is encoded by a single gene mapped to human chromosome 17q21 and is highly regulated by protein kinases such as protein kinase-A, calmodulin-dependent kinase II, and proteinkinase C (PK-C) (de Reus et al. 2024). GFAP is expressed by numerous cell types in the CNS, including astrocytes and ependymal cells during development.

GFAP has been studied in the context of brain disorders, such as multiple sclerosis and neuromyelitis optica, which target astrocytes. Elevated blood levels of GFAP have been found in neuroinflammatory diseases (Shaygannejad et al. 2024). GFAP has also been identified as a potential biomarker protein for neurodegenerative diseases, including Parkinson's disease (de Reus et al. 2024).

In AN, GFAP levels have been found to be significantly increased in acutely underweight patients compared to HCs, with subsequent normalisation after partial weight restoration (Hellerhoff et al. 2021). Interestingly, GFAP showed a negative association with age in AN patients-a finding contrary to the typical positive correlation observed in healthy populations-potentially indicating disrupted maturational processes in astrocytes during severe malnutrition. The decrease in GFAP levels with weight gain correlates with improvements in BMI, suggesting that astroglial damage processes may be reversible with nutritional rehabilitation. Since there has been only one study, this finding must be interpreted with caution.

3.4. Hypothalamic signalling molecules associated with the regulation of appetite and metabolism

The Y neuropeptide family, comprising neuropeptide Y (NPY) and peptide YY (PYY), has been hypothesised to play a significant role in the aetiology of EDs. These peptides are key regulators of food intake and metabolic processes, acting at both central and peripheral levels, and are involved in gut-brain signalling pathways.

3.4.1. Neuropeptide Y

NPY is primarily synthesised and functions in the brain, where it plays a crucial role in regulating appetite and energy homeostasis. It stimulates hunger, decreases energy expenditure, and promotes weight gain. During periods of food deprivation, NPY secretion is elevated, which leads to increased food intake and preferential carbohydrate consumption to restore energy balance. Leptin, a critical regulator of energy homeostasis, is a potent inhibitor of NPY secretion. Studies examining fasting serum NPY concentrations in patients with AN have yielded inconsistent results: some found decreased levels (Baranowska et al. 2001; Tyszkiewicz-Nwafor et al. 2021), while others showed elevated levels (Jagielska et al. 2013; Sedlackova et al. 2012; Sedlackova et al. 2011), and yet others found normal levels (Baranowska et al. 1997; Galusca et al. 2015). Furthermore, several studies have observed no alterations in NPY concentrations postprandially (Sedlackova et al. 2012; Sedlackova et al. 2011). In contrast, early cross-sectional studies assessing NPY in CSF consistently reported elevated levels in patients with AN compared to controls, with no normalisation after partial weight restoration, suggesting a possible central dysregulation of NPY (Kaye et al. 1990).

3.4.2. alpha-MSH

Alpha-Melanocyte Stimulating Hormone (α-MSH) is a neuropeptide derived from proopiomelanocrotine (POMC) that activates the melanocortin 4 receptor. Beyond its action on inducing melanin synthesis, α-MSH is known for its anorexigenic action and is usually decreased during undernutrition (Fan et al. 1997) as a consequence of a reduced leptin signalling (Seeley et al. 1997). Two studies found lower α-MSH levels in AN compared to HCs (Galusca et al. 2015; Roubalova

et al. 2021). However, two other studies reported no differences (Moriya et al. 2006). According to a longitudinal study in 40 patients, α-MSH levels could vary depending on patient nutritional status and be lower in acute stages but restored after weight regain (Seitz et al. 2024). Two studies identified increased levels of antibodies reactive to α-MSH in patients with AN (Fetissov et al. 2002; Escelsior et al. 2022). For more detailed information on the influence of immunoglobulins on α-MSH signalling see Section 3.9.2.

Interestingly a preclinical study showed that activation of the melanocortin-4-receptor (MC4R) with α-MSH could increase running wheel activity and decrease food intake in animal model of AN offering a potential mechanistic underpinning to its role in AN (Hillebrand et al. 2005).

3.4.3. Neuropeptide B (NPB) and neuropeptide W (NPW)

Neuropeptide B (NPB) and neuropeptide W (NPW) are endogenous ligands of the G protein-coupled receptors (GPR) GPR7 and GPR8, but their precise roles in humans are not fully understood. NPB is produced in amygdala, hypothalamic nuclei, and pancreatic islets; NPW is produced in neurons within the hypothalamus and brainstem. Animal studies suggest that these neuropeptides may be involved in energy homeostasis and regulation of the hypothalamic-pituitary-adrenal (HPA) axis. To date, only two studies have investigated NPB and NPW in patients with acute AN. These studies reported elevated levels of NPB and normal levels of NPW (Grzelak et al. 2018a). Additionally, during nutritional rehabilitation, NPB concentrations decreased, while NPW levels remained unchanged (Grzelak et al. 2018b).

3.4.4. Kisspeptin (KISS)

Kisspeptin (KISS) is primarily produced in the arcuate nucleus and the anterior ventral periventricular nucleus of the hypothalamus. It is a ligand for the KISS1R receptor, which plays a crucial role in regulating the ovarian cycle and the gonadal axis. It is suggested that KISS neurons project axons to the arcuate nucleus, where they directly stimulate POMC/CART neurons and indirectly inhibit NPY/ agouti-related protein (AgRP) neurons. This in turn suggests that KISS neurons integrate peripheral metabolic signals, influencing the reproductive hormone axis, and may also serve as natural satiety signals. In studies of people with AN, some show normal KISS levels (Pałasz et al. 2021; Podfigurna et al. 2018), while others report lower serum levels in typical AN and higher levels in AAN (Bacopoulou et al. 2017). Pałasz et al. (2021) showed no significant differences between malnourished AN patients, partially weight restored AN patients, or HC. Also in patients with AN, KISS has been positively correlated with BMI and, inversely, with physical activity (Bacopoulou et al. 2017).

3.4.5. Spexin (SPX)

Spexin (SPX), a highly conserved peptide from the galanin/KISS family, regulates reproductive processes, gastrointestinal activity, and cardiovascular function. Animal studies have shown that exogenous SPX reduces food intake and body weight, possibly inducing satiety by inhibiting NPY and orexin. SPX also increases locomotion and lipid oxidation and improves glucose tolerance (Kumar et al. 2021; Türkel et al. 2022).

3.4.6. Phoenixin (PNX)

PNX is a reproductive hormone involved in regulating the hypothalamus–pituitary–gonadal (HPG) axis, partly through its interactions with KISS. Its expression in several nuclei related to food intake regulation suggests its involvement in these processes. PNX is secreted in the gastrointestinal tract, potentially playing a role in the gut-brain axis. In AN patients, PNX concentrations were lower in malnourished adolescents and increased during weight normalisation (Pałasz et al. 2021).

3.4.7. Orexin

Orexins/hypocretins are neuropeptides implicated in numerous processes, including food intake, sleep quality and cognition. Findings on plasma orexin levels are inconsistent (Bronsky et al. 2011; Steward et al. 2019). In a longitudinal study with 36 girls with AN and 14 HCs, where orexin levels were elevated in girls with AN compared to HCs, orexin levels of girls with AN were comparable to those of HCs after 8 weeks of re-alimentation (Bronsky et al. 2011).

There is general agreement that orexins, especially Orexin-A, have a role in arousal and the sleep-wake cycle, and their involvement in narcolepsy was well documented (Mogavero et al. 2023; Mohammadi et al. 2021), even as replacement therapy strategy (Thomaz et al. 2024). People with AN experience poorer sleep quality than in HC (Sauchelli et al. 2016), and this was found to be associated with concentrations of orexin-A; both were found to be predictors of poorer treatment outcome.

3.4.8. Endocannabinoid system

The endocannabinoid system is a complex signalling system that modulates the central nervous system

(CNS). It is made up of endogenous ligands (endocannabinoids, or eCBs), specific receptors, and the enzymatic machinery responsible for metabolising them. The two eCBs that have been most extensively studied are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These are lipids that are derived from polyunsaturated fatty acids and synthesised from membrane phospholipid precursors. Their production is triggered in an activity-dependent manner, typically in response to intracellular increases in calcium ions (Ca^{2+}) associated with the activation of metabotropic or ionotropic receptors. The synthesis of AEA and 2-AG is mediated, respectively, by N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL). In the CNS, eCBs are synthesised postsynaptically and released locally in response to physiological or pathological stimuli, acting retrogradely on presynaptic terminals. Brain concentrations of 2-AG are significantly higher than those of AEA. These compounds are mainly degraded by fatty acid amide hydrolase (FAAH), which hydrolyses AEA, and monoacylglycerol lipase (MAGL), which degrades 2-AG.

The two main receptors of the eCB system are cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R). Both are coupled to G proteins. CB1R is predominantly found in the CNS, particularly in GABAergic and glutamatergic neurons. It is involved in processes such as motor control, emotion, cognition, body temperature regulation, appetite, and energy homeostasis. CB1Rs are also found in peripheral tissues such as skeletal muscle, adipose tissue, adrenal glands, gastrointestinal tract, gonads, and immune cells.

The CB2 receptor is predominantly localised in immune system cells and haematopoietic tissues. Although AEA and 2-AG share receptors, they are not functionally equivalent and can induce different biological responses. AEA acts as a partial agonist of CB1R and a weak agonist of CB2R, whereas 2-AG behaves as a full agonist of both. In addition to specific enzymes and receptors, both compounds can be metabolised by other enzymes, such as cyclooxygenase-2 (COX-2) and cytochrome P450, and other non-cannabinoid receptors that are potentially involved in signalling these ligands have also been proposed. These include the orexin type 1 receptor (OX1R) and the serotonin 5-HT2A receptor (5-HT2R), which broadens the functional spectrum of the system.

The eCB system acts as a key modulator of neurotransmission. By acting on presynaptic receptors, it inhibits the release of both excitatory (glutamate) and inhibitory (γ-aminobutyric acid; GABA) neurotransmitters in a retrograde manner. Activation of CB1R triggers several intracellular cascades, resulting in hyperpolarisation of the presynaptic neuron and inhibition of neurotransmitter exocytosis. The functional translation of this system involves its participation in a wide range of physiological and pathological processes at both the central and peripheral levels, including neurodevelopment, synaptic plasticity, nociception, thermoregulation, neuroprotection, immunomodulation, inflammation, the regulation of emotions and cognition, motor activity and cell proliferation, as well as the control of energy intake and homeostasis. At a central level, the eCB system modulates the circuits that regulate appetite, including the homeostatic pathway at the hypothalamic level and the hedonic pathway associated with the dopaminergic reward system, which has a predominantly orexigenic function. At a peripheral level, the eCB system regulates energy storage and mobilisation by acting on metabolically active tissues, such as adipose tissue, skeletal muscle, and the gastrointestinal tract. This contributes to the neuroendocrine integration of energy balance.

The involvement of the eCB system in extreme weight and feeding situations (from obesity to AN) has aroused great interest, given its physiological role in modulating feeding behaviour and energy metabolism (D'Addario et al. 2014; Solinas et al. 2008). The seminal study in rodents by Kirkham et al. (2002) demonstrated that under normal conditions there is an increase in fasting brain AEA and 2-GA concentrations, with a subsequent return to basal levels during feeding and in the postprandial state. In humans, studies investigating the functionality of the eCB system in non-clinical populations have shown an increase in plasma concentrations of 2-AG and AEA prior to food intake (Monteleone et al. 2012), particularly with exposure to highly palatable foods (Monteleone et al. 2012). In the postprandial phase, a reduction in circulating concentrations of AEA and 2-AG has been observed, although it varies depending on the palatability of the food and the type of eCB (Monteleone et al. 2015). In this regard, a positive correlation has been described between limbic concentrations of dopamine and eCBs and craving for highly palatable foods, reinforcing their involvement in food-related reward seeking behaviour (DiPatrizio 2014).

Several studies suggest the hypothesis that dysfunction of the eCB system could underlie maladaptive behaviours related to food intake, related cognitive aspects and body fat mass distribution (Monteleone et al. 2005; Pastor et al. 2016). Higher basal plasma concentrations of AEA and/or 2-AG have been observed in people with obesity, and it has been suggested that the increase in these concentrations may even precede the onset of obesity, being higher than those observed

in participants with lower BMI, such as HC and AN (Baenas et al. 2023).

In a pioneering study in EDs, Monteleone et al. (2005) described an increase in fasting circulating AEA in AN and BED. However, no differences in plasma 2-AG levels were found compared to HCs. Changes in peripheral AEA levels were positively correlated with subjects' ratings of the urge to eat and enjoyment of the food presented. Again, plasma 2-AG levels did not differ significantly, regardless of meal type. Contrary to what happens in obesity, hypoactivation of the eCB system has been suggested to occur in AN (Baenas et al. 2023; Monteleone et al. 2005), when compared to the HC group, with lower levels of AEA during fasting. When considering clinical and psychopathological symptoms in AN (Baenas et al. 2023), AEA was associated with emotional dysregulation, whereas 2-AG was associated with general psychopathology. However, some results in the literature show discrepancies and opposite findings (Piccolo et al. 2020).

In this regard, neuroimaging studies have analysed the association between circulating levels of eCBs and brain functional connectivity, specifically in the nucleus accumbens (NAcc) region (Miranda-Olivos et al. 2023). They found that functional connectivity in the NAcc insula mediated the association between AEA concentrations and BMI in the AN group.

3.5. Gastrointestinal signalling molecules associated with regulation of appetite and metabolism

3.5.1. Ghrelin

Ghrelin is an appetite regulatory hormone that signals the hypothalamus to increase appetite and stimulates the pituitary gland to produce and release crucial hormones. Ghrelin levels undergo an ultradian secretion pattern increasing during fasting and decreasing after a meal. Meta-analytical evidence suggests ghrelin levels may be higher in patients with AN, including ghrelin's acyl-ghrelin and desacyl-ghrelin forms (Seidel et al. 2021). The same meta-analysis shows that total ghrelin levels decreased with follow-up in longitudinal studies. Similar observations have been made for desacyl-ghrelin with higher levels in patients with AN. Longitudinal studies show a decrease of desacyl-ghrelin but not acyl ghrelin between inclusion and follow-up (Duriez et al. 2020; Grigioni et al. 2022; Koyama et al. 2010; Uehara et al. 2005). In Seidel et al. (2021), pooled data from five studies showed no significant difference in acyl ghrelin between pre-treatment and follow-up.

Other studies have shown that acyl-ghrelin was increased in AN individuals compared to HCs which they linked with the acute stress induced to participants (Westwater et al. 2021). More studies have confirmed these findings, in both fasting and postprandial states (Dutkiewicz et al. 2022; Mancuso et al. 2020). Ghrelin levels were also correlated with the type and preference of food consumed (i.e. satiated acute AN had lower ghrelin levels after food consumption; while satiated recovered AN had higher ghrelin levels after consuming preferred food but lower ghrelin levels after consuming non-preferred food) (Monteleone et al. 2016a). Therefore, ghrelin has different qualities making it a possible biomarker assessing the success of treatment, though more research is needed

Ghrelin may have a role beyond appetite regulation, particularly in the modulation of reward-oriented behaviour (Al Massadi et al. 2019). Ghrelin is recognised as a proimpulsive peptide increasing impulsive and compulsive-like behaviour in rodents. Interestingly, patients with acute AN exhibit a negative correlation between ghrelin levels and sensitivity to delayed gratification, a core feature of reward alterations in AN, whereas a positive correlation was found in remitted AN and HCs (Bernardoni et al. 2020). Therefore, the normalisation of the interplay between metabolic markers of appetite and reward-oriented behaviour could be one of the footprints of remission in AN.

Finally, an association between lower ghrelin levels, poor inhibitory control and higher ED-related psychopathology has been described in patients with AN. In their findings, Paslakis et al. (2019) further describe that although they did not find a direct association between ghrelin levels and executive dysfunction, both variables may act as mediators in the pathogenesis of AN, as patients with AN and lower ghrelin levels appear to be more severely ill and have more impaired decision making (Paslakis et al. 2019).

Measuring ghrelin can be challenging in clinical settings as acyl ghrelin is rapidly degraded into desacyl form by several plasmatic esterase and specific treatment conditions are necessary to ensure stability (Theofanopoulou et al. 2022). Moreover, both nutritional state (i.e. BMI) and feeding state (sated of fasted condition, duration of overnight fast, meal composition) influence plasma ghrelin accounting for high heterogeneity between studies. The dynamic analysis of the kinetics of regulation of ghrelin before and after a meal could help overcome these limitations. Therefore, ghrelin has different qualities making it a possible biomarker assessing the success of treatment, while there

is still a need for additional investigations to support its informativity in different settings and subtypes of the disorder.

3.5.2. LEAP-2

Liver Expressing Antimicrobial Peptide 2 (LEAP-2) has recently been identified as a new actor in the ghrelin system with antagonistic action on the ghrelin receptor, counteracting the orexigenic effect of ghrelin in mice and humans (Ge et al. 2018; M'Kadmi et al. 2019). Plasma levels of LEAP-2 are elevated in overweight and obese adults, and correlate with BMI, suggesting opposite regulation between LEAP-2 and ghrelin (Andreoli et al. 2024; Mani et al. 2019). With its antagonistic action on the ghrelin system, LEAP-2 is now identified as an anorexigenic peptide. Indeed, central and peripheral infusions of LEAP-2 lead to an inhibition of ghrelin-induced food intake in mice (Ge et al. 2018; Hagemann et al. 2022; Mani et al. 2019). Similarly, LEAP-2 infusion induces a spontaneous decrease of caloric intake during free meals in healthy males (Hagemann et al. 2022) and post prandial increase of LEAP2 has been implicated in eating behaviour suppression (Bhargava et al. 2023). Recent evidence showed that central LEAP-2 injections lead to the reduction of reward-oriented behaviour towards food cues, decreasing food palatability through dopamine modulation (Tufvesson-Alm et al. 2024).

So far, one study has explored the regulation of LEAP-2 in a longitudinal evaluation of 30 patients with AN at various nutritional levels (i.e. undernourished and refed after a four-month inpatient program). Results showed unexpectedly higher LEAP-2 levels in undernourished AN patients compared to those in the refed state, suggesting a potential abnormal regulation of LEAP-2 with energy state in AN (Du Montcel et al. 2023). Interestingly, patients exhibiting this dysregulation of LEAP-2 had an increased risk of relapse at six months (i.e. BMI< 18.5 kilograms per square metre [kg/m^2]). With effects of regulating appetite and food reward, disrupted regulation of LEAP-2 could be a risk factor of relapse through inappropriate signalling of the energy state that would increase the rapid weight loss. These results have not yet been replicated, but identifying patients exhibiting such dysregulated profiles could be considered as a potential promising biomarker.

3.5.3. GLP-1

Glucagon-Like Peptide-1 (GLP-1) acts as an appetite suppressor that releases signalling through the vagal nerve and is negatively correlated with body weight (Smith and Moran 2021). No difference in GLP-1 levels was detected between testing groups and AN individuals (Stengel et al. 2014; Westwater et al. 2021). This was also supported by a study that showed no correlation between GLP-1 levels and body weight (Stengel et al. 2014). Other evidence has shown an increase in GLP-1 in patients with AN compared to constitutionally thin subjects and HCs (Germain et al. 2007; Heruc et al. 2018b). After refeeding, GLP-1 levels were significantly higher when compared to baseline (Heruc et al. 2018b). Both the levels of GLP-1 in AN individuals and the response of food consumption and weight restoration on GLP-1 levels warrant more investigations. Of note, GLP-1 agonist treatment of individuals with obesity and a history of AN has been associated with relapse of the AN (Guerdjikova et al. 2024).

3.5.4. Cholecystokinin

Cholecystokinin is a hormone secreted by cells in the small intestine and is responsible for the stimulation of release of bile acids to promote fat digestion as well as stimulation of secretion of pancreatic enzymes. Its role in appetite regulation includes acting as a satiety signal hormone. Most evidence suggests cholecystokinin is increased in individuals with AN relative to HCs (Philipp et al. 1991; Geracioti et al. 1992; Tamai et al. 1993; Fujimoto et al. 1997; Tomasik et al. 2005). Although cholecystokinin is considered a biomarker of satiation in healthy individuals, its use as a biomarker for AN needs further investigations.

3.5.5. Peptide YY

Primarily secreted in the gastrointestinal system, PYY plays a key role in central and peripheral appetite regulation. PYY signals meal termination, reduces food intake, and slows gastrointestinal motility. It functions as a satiety signal by inhibiting the production of ghrelin. Studies of fasting serum PYY concentrations in patients with AN exhibit mixed results. Some studies report no significant differences compared to HCs (Otto et al. 2007; Sedlackova et al. 2012; Tam et al. 2020; Tyszkiewicz-Nwafor et al. 2021), while others document elevated levels (Misra et al. 2006; Nakahara et al. 2007; Pfluger et al. 2007; Lawson et al. 2011; Heruc et al. 2018a; Mancuso et al. 2020). During nutritional rehabilitation, PYY concentrations have been found to either remain unchanged (Tam et al. 2020) or decreased (Heruc et al. 2018a). Postprandially, PYY levels increased in some studies (Nakahara et al. 2007; Otto et al. 2007; Sedlackova et al. 2012), while others reported stable levels (Stock et al. 2005). In addition, in

adults with AN, higher circulating PYY has been associated with increased HPA drive and with greater disordered-eating psychopathology, independent of BMI (Lawson et al. 2011).

PYY has also been linked to the capacity for smell and taste, and has been suggested to modulate taste responsiveness (La Sala et al. 2013). In a study analysing differences in smell and taste capacity between woman with extreme weight conditions, higher odour threshold scores (i.e. greater olfactory capacity) were associated with higher PYY levels in a subsample of patients with AN (Fernández-Aranda et al. 2016). Interestingly, results also showed that this greater smell capacity was an indirect indicator of ED severity (Fernández-Aranda et al. 2016).

3.6. Signalling molecules from adipose tissue

3.6.1. Leptin

Leptin was discovered in 1994 (Zhang et al. 1994) as the first out of currently more than 600 known adipokines (Kirichenko et al. 2022), which underscores adipose tissue's role as the largest endocrine organ. The clinical phenotypes of the *ob/ob* mouse and of humans harbouring mutations in the leptin gene precluding the expression of functional leptin are characterised by a voracious appetite, early onset extreme obesity, hypothalamic hypogonadism and impaired immunity (Farooqi and O'Rahilly 2009; Friedman 2019).

In ob/ob mice, all psychological and somatic symptoms of congenital leptin deficiency can be treated successfully by application of exogenous leptin (Farooqi and O'Rahilly 2009; Friedman 2019). In humans, recombinant human leptin (metreleptin) normalises hunger and satiety within hours to days after its first application; long-term supplementation entails significant weight loss and achievement of adult reproductive status (Farooqi and O'Rahilly 2009). Systematic psychological studies on the effect of treatment with recombinant human leptin have not been conducted; preliminary evidence suggests that mood may improve (Hebebrand, Zorn, et al. 2022; von Schnurbein et al. 2023). In adults, treatment with recombinant leptin has led to volume increments of specific brain regions (Matochik et al. 2005).

Circulating leptin levels correlate with BMI (kg/m^2) and, even more so, with adipose tissue mass (Considine et al. 1996; Terra et al. 2013). Persons with obesity have high serum leptin levels, whereas lean people have low leptin levels. Indeed, there is substantial variation in leptin secretion for any percentage of body fat. Throughout adolescence serum leptin increases in females only; adult females have two to three times higher leptin levels than males (Hebebrand, Plieger, et al. 2024). As demonstrated in meta-analyses, individuals with AN have sub-physiological levels (hypoleptinaemia) (Cassioli et al. 2025; Karageorgiou et al. 2020; Wu et al. 2024). In contrast, the soluble leptin receptor, which binds leptin in serum, is increased (Wu et al. 2024), thus further reducing the bioavailability of leptin in AN (Hebebrand, Plieger, et al. 2024).

In the early 2000s, clinical trials failed to show a substantial weight reducing effect of metreleptin in patients with multifactorial obesity revealing that an elevation of an already high leptin secretion in such patients does not reduce appetite or body weight; only patients with the lowest leptin levels lost more than ten percent of their weight (Depaoli et al. 2018). Accordingly, the primary role of leptin as an anorexigenic/satiety hormone has been questioned (Flier and Maratos-Flier 2017). Instead, evidence has accumulated that leptin is the key hormone to both centrally and peripherally regulate the adaptation to starvation based on a simple feedback mechanism (Ahima et al. 1996; Hebebrand, Hildebrandt, et al. 2022). The reduction of adipose tissue mass induced by a prolonged reduced energy intake results in hypoleptinaemia, thereby altering the function of both peripheral and central tissues to increase the likelihood of survival mostly by reducing energy expenditure. All hypothalamic-pituitary-end organ axes are up- or down-regulated by hypoleptinaemia (Ahima et al. 1996).

Examples of somatic functional implications of reduced central and/or peripheral leptin signalling include amenorrhoea, bradycardia, hypotonia, hair loss, and reduced bone density and haematopoiesis (Hebebrand, Plieger, et al. 2024). As leptin interacts in concert with gonadotropins and the growth hormone axis to initiate the physiological changes of puberty, decrease in leptin may account for the delay or interruption of sexual maturation characteristic of adolescent AN. Additionally, leptin contributes to preserve adequate reproductive functions by stimulating the activity of the gonadotropic axis (Ahima et al. 1996).

Apart from reducing energy expenditure, hypoleptinaemia increases the sensitivity of sweet receptors in the tongue and slows gastrointestinal motility entailing both a rapid feeling of fullness upon food intake and constipation (Hebebrand, Hildebrandt, et al. 2022). Increased running wheel activity in food-restricted rats, potentially reflecting food foraging behaviour, has causally been linked to hypoleptinaemia (Hebebrand et al. 2019). In patients with AN, the relationship between hyperactivity and leptin might correspond to an inverted U with its occurrence dependent on serum levels in the range of approximately 0.5 to 2.0

nanograms per millilitre (ng/ml) (Holtkamp et al. 2006; Hebebrand et al. 2019).

Evidence from both rodents and humans suggests that psychological symptoms of starvation such as fatigue, insomnia, depressed mood, reduced libido, and constant preoccupation with food are mediated by hypoleptinaemia (Hebebrand, Hildebrandt, et al. 2022). In patients with AN, premorbid BMI strongly predicts weight loss, suggesting that 'entrapment' in this disorder may be triggered by an amount of weight loss sufficient to induce hypoleptinaemia (Hebebrand, Seitz, et al. 2024). Off-label metreleptin treatment of patients with AN and AAN has been found to result in a reduction of starvation psychological symptoms within one to five days upon dosages ≥ 6 milligrams per litre (mg/l), the response varying between patients (Hebebrand, Hildebrandt, et al. 2022; Hebebrand, Plieger, et al. 2024). In some patients, weight phobia also declined. Clinical trials are required to validate these findings and to determine if leptin substitution will, in the medium term, facilitate weight gain.

Leptin is also a potent neurotrophic factor (Bouret 2010). It mediates volume increases of amygdala and hippocampal and thalamic nuclei during weight gain in patients with AN (Wronski et al. 2023a, 2023b, 2024; Bahnsen et al. 2024; Wronski et al. 2025) In both mice (Ahima et al. 1999) and humans (Matochik et al. 2005) with congenital leptin deficiency, treatment with recombinant leptin increases volumes of specific brain regions as well as whole brain volume.

To summarise, leptin (perhaps in combination with other adipokines) may prove to be a crucial endocrine mediator of 'entrapment' in AN (Hebebrand et al. 2023) caused by a sufficient amount of weight loss (Hebebrand, Plieger, et al. 2024; Hebebrand et al. 2025). Reduced leptin signalling in AN is causally involved in the emergence of somatic and psychological symptoms of starvation (Hebebrand, Plieger, et al. 2024). Considering the effect of food restriction induced hypoleptinaemia on the hypothalamus-pituitary-end organ axes (Ahima et al. 1999), leptin may act as a master switch underlying multiple endocrine alterations in patients with acute AN (Hebebrand, Plieger, et al. 2024). Vice versa, weight gain induced increments in leptin secretion might underlie the slow resolution of such symptoms. Indeed, complete resolution of mental symptoms requires normalisation of the size of particular brain nuclei (Wronski et al. 2023a, 2023, 2024, 2025; Bahnsen et al. 2024). Additionally, risk of relapse is decreased in patients with higher leptin levels after achievement of target weight (Sala et al. 2023). Measurement of leptin levels at baseline predicts fat mass (Mathiak et al. 1999). The level in acute AN may help to differentiate constitutional thinness from AN with a leptin level < 2 ng/ml and > 4 ng/ml being consistent with acute AN and constitutional thinness, respectively (Föcker et al. 2011).

3.6.2. Adiponectins

Adiponectins are signalling proteins secreted by adipose tissue that play a crucial role in regulating metabolism, inflammation, and immunity. They have been evaluated in different study designs including meta-analyses (Karageorgiou et al. 2020; Tural and Iosifescu 2022). Two meta-analyses including AN and AN-BP and AN-R subtypes of AN, respectively, found greater adiponectin levels in people with AN compared to HCs (Karageorgiou et al. 2020; Tural and Iosifescu 2022). Other evidence from longitudinal studies accords with these meta-analytical findings (Andries et al. 2015; Tyszkiewicz-Nwafor et al. 2019; Calikoglu et al. 2024). However, some evidence revealed that weight restoration had no clear effect on the normalisation of adiponectin levels (Andries et al. 2015; Tyszkiewicz-Nwafor et al. 2019). The results suggest the role of adiponectin as a crucial molecule in balancing the metabolism, and a potential role of adiponectin to act as a biomarker of the disorder. However, many other molecules are found to be disturbed in AN and a full profile of the metabolic changes would aid in the diagnosis of the disorder. More evidence would be necessary to give solid conclusions.

3.6.3. Resistin

Resistin is a hormone that is produced by immune cells and associated with inflammation and a range of different diseases. A regression analysis showed a link between adiponectin and resistin where resistin acted like a significant modifier for adiponectin (Tural and Iosifescu 2022). The hormone resistin is showing some pre-elementary evidence to be utilised as a biomarker of the disorder. However, this hormone is found to be significantly lower in patients with AN when compared to HCs [−1.67 (−2.85, −0.48)] in a meta-analysis of 20 studies (Karageorgiou et al. 2020). Additional evidence has shown that it remained lower in recovered individuals with AN comparing to HCs (Tyszkiewicz-Nwafor et al. 2019) while some evidence shows that although plasma resistin was lower in AN individuals, the subcutaneous adipose tissue resistin was significantly higher in AN than HCs (Dostalova et al. 2006).

3.6.4. Vaspin

Vaspin is a regulatory hormone secreted by adipose tissue that is involved in insulin sensitivity.

Meta-analytical evidence from 3 studies found a significant increase in serum vaspin levels in AN individuals compared to HCs (Karageorgiou et al. 2020). Other cross-sectional and longitudinal evidence supports the findings of the meta-analysis and shows an increase in both serum and salivary vaspin levels (Ostrowska et al. 2016; Oświęcimska et al. 2016; Grzelak et al. 2018b; Paszynska et al. 2018). Serum vaspin normalised following treatment, suggesting endocrine system involvement (Grzelak et al. 2018b).

3.6.5. Omentin

Omentin is an adipokine mainly produced by visceral adipose tissue. Omentin is expressed in two isoforms, omentin-1, which is the main circulating form in human plasma, and omentin-2 which is released in the intestinal lumen and has not been detected in plasma (Tan et al. 2010). Higher omentin levels are seen in individuals with AN while the lowest are seen in patients with obesity (Calikoglu et al. 2024). Other conflicting findings found no differences in omentin levels in acute AN and partially recovered AN (Tyszkiewicz-Nwafor et al. 2021). Therefore, available evidence does not support its use as a biological marker in AN.

3.6.6. Visfatin

Visfatin is a regulatory hormone that reduces glucose release from the liver and triggers use of glucose stored in fat and muscle cells. A meta-analysis of five studies found lower serum/plasma levels of visfatin in people with AN compared to HC, but this difference was not significant, and there was high heterogeneity across studies (Karageorgiou et al. 2020). Additional studies have shown inconsistent findings that do not accord with the above meta-analytical findings (Dostálová et al. 2009; Ostrowska et al. 2014; Seidel et al. 2015; Ostrowska et al. 2016; Baranowska-Bik et al. 2017). Studies were also inconsistent in terms of the effect of weight restoration and treatment on the levels of visfatin in AN individuals (Dostálová et al. 2009; Seidel et al. 2015; Tyszkiewicz-Nwafor, Dutkiewicz, et al. 2021).

3.6.7. Obestatin

The anorexigenic appetite regulatory hormone, obestatin, which is produced in the gastrointestinal tract was discovered in 2005 and therefore considered to be a relatively recently discovered hormone (Zhang et al. 2005). It plays a crucial role in the course of AN as this hormone is food consumption dependant. In acute AN, the levels of obestatin were found to be higher relative to partially treated individuals with AN (Monteleone et al. 2008; Dutkiewicz et al. 2022). Weight restoration showed an effect on the hormone levels. However, supporting evidence is still needed to confirm the usefulness of this hormone as a biomarker for AN.

3.6.8. Apelin

Apelin has a crucial role in the activation of signal transduction in human cells and in promoting food intake (Yan et al. 2020). In the AN literature, apelin was only looked at briefly and found to be significantly higher than in individuals with obesity (Calikoglu et al. 2024). Apelin levels decreased after the initiation of the treatment, which may be linked with adipose tissue mass (Calikoglu et al. 2024).

3.6.9. Betatrophin

Betatrophin is a relatively recently described hormone that is expressed in adipose tissue and liver and plays a key role in glucose tolerance, lipid metabolism and diabetes. The relationship between betatrophin and obesity/metabolic disorders has been well documented (Ye et al. 2019). The few studies that have examined it in AN found that plasma betatrophin levels were elevated compared to those in HCs, while in women with morbid obesity, levels were significantly reduced (Barja-Fernández et al. 2015). This suggests an inverse regulatory effect between plasma betatrophin concentrations and BMI, and its possible involvement in lipid metabolism.

3.6.10. Irisine

Irisine is a myokine (hormone released by muscles during exercise and expressed in adipose tissue) that plays a key role in the regulation of metabolism and energy expenditure. It has been extensively described in the obesity and cardiometabolic literature (Torabi et al. 2024). When it was analysed in extreme weight conditions, including AN and obesity, considering resting exercise expenditure (REE), physical activity and irisin blood concentrations (Stengel et al. 2013; Pardo et al. 2014), it was found that AN showed similar levels than HC and lower levels than participants with obesity. Among the groups, irisin levels were inversely correlated with daily physical activity and directly correlated with REE. Particularly in AN, the results were not conclusive and did not show clear correlations with activity levels (Hofmann et al. 2014).

3.7. Stress-related hormones

The HPA axis is the main component of the endogenous stress response system responsible for the 'slow' response to real or perceived environmental stressors *via* the secretion of glucocorticoids (Tsigos and Chrousos 2002). The hypothalamic paraventricular nucleus (PVN) is a key component of the HPA axis, since PVN neurons release corticotropin-releasing hormone (CRH) (and arginine vasopressin) into the portal circulation. CRH stimulates corticotrophin cells in the anterior pituitary gland to synthesise and secrete adrenocorticotropic hormone (ACTH) into the systemic circulation. ACTH, in turn, stimulates secretion of cortisol from the adrenal cortex. Cortisol negatively regulates CRH and ACTH synthesis and secretion (De Kloet et al. 1998).

3.7.1. CRH and ACTH

The HPA axis has been the focus of extensive research in people with AN with mixed findings (Lo Sauro et al. 2008; Schorr et al. 2015; Culbert et al. 2016).

Two initial studies reported increased levels of CRH in the spinal fluid of patients with AN in the acute phase of the illness but not after weight restoration (Kaye et al. 1987; Walsh et al. 1987). Regarding peripheral ACTH levels, a recent meta-analysis (Wu et al. 2024) confirmed that blood levels of ACTH are significantly higher in adult people with AN compared to HCs.

3.7.2. Cortisol

Cortisol is the principal glucocorticoid secreted in response to a stressor in humans: it promotes gluconeogenesis and lipolysis in the liver and adipose tissue to provide the energy necessary to cope with the stressor. Following its secretion cortisol exerts negative feedback on HPA axis activity to stop its own secretion and terminate the stress response to minimise its catabolic, lipogenic, anti-reproductive and immunosuppressive actions, which have long-term deleterious effects on the organism (Adam and Epel 2007; Habib et al. 2001). Secretion of cortisol can be assessed in basal conditions and after stimulation or inhibition tests providing information on the tonic and dynamic functioning of the HPA axis, respectively. Baseline assessment of cortisol production can be performed by different techniques: a) measurement of the 24-hour pooled serum cortisol level, which provides an estimation of the total cortisol secreted over the 24-hour period; b) 24-hour urinary cortisol assessment, which measures the amount of free cortisol excreted in the urine over the 24-hour period; and c) measurement of time-specific cortisol levels in blood or other biological fluids with serum morning cortisol assessment being the most common procedure. Dynamic evaluation of cortisol production is often obtained by measuring peripheral cortisol secretion levels after either pharmacologic tests or stress evoking laboratory paradigms. The most common pharmacological test is the dexamethasone suppression test (DST), which measures circulating cortisol levels in the morning after the administration of dexamethasone at 11:00 PM (individuals with HPA axis hyperactivity escape the suppression of morning cortisol levels). Among laboratory stress paradigms, the Trier Social Stress Test (TSST). Allen et al. (2017) measures cortisol response to an acute social challenge and is widely used. An intermediate strategy between basal and dynamic tests of HPA axis functioning is represented by the saliva Cortisol Awakening Response (CAR) (Stalder et al. 2016), which measures the increase in saliva cortisol levels occurring approximatively 30 min after awakening in the morning and can be considered either a basal measure or a measure of the HPA axis reactivity to awakening.

To date, three meta-analyses of studies assessing baseline cortisol levels (Bailly et al. 2021b; Thavaraputta et al. 2023; Wu et al. 2024) and one meta-analysis of studies measuring cortisol reactivity in response to an interpersonal stressor (Monteleone et al. 2018) have been conducted. Indeed, Bailly et al. (2021b) found that the 24-hour mean cortisol level was significantly higher in individuals with AN compared to both HCs and individuals with constitutional thinness. Thavaraputta et al. (2023) reported that in people with acute AN: 1) mean serum morning cortisol levels were higher than in HCs with a pooled mean difference (MD) of 4.58 milligrams per decilitre (mg/dL); 2) 12-hour and 24-hour pooled serum cortisol levels were significantly increased compared to HCs with pooled MD of 3.08 mg/dL and 7.23 mg/dL, respectively; 3) mean 24-hour urinary cortisol levels were significantly higher compared to HCs with a pooled MD of 30.06 milligrams per day (mg/day); 4) mean serum cortisol level measured in the morning after low-dose DST was significantly higher in AN than in HCs with a pooled MD of 5.4 mg/dL. Wu et al. (2024) confirmed that adults with AN had higher peripheral cortisol levels than HCs. All meta-analytic studies included patients in the acute phase of AN and meta-analyses of studies assessing baseline HPA axis functioning in individuals recovered from AN are lacking. This is an important limitation since several, although not all studies (Lo Sauro et al. 2008; Culbert et al. 2016), have found that

increased cortisol levels in underweight patients with AN normalise after body weight gain. Given this preliminary evidence, it can be argued that the hypercortisolism of individuals with acute AN is a state-dependent phenomenon likely due to the effects of starvation or malnutrition on the HPA axis *via* an increased release of CRH (Gold et al. 1986).

As for dynamic assessment of cortisol production in AN, a meta-analysis of 16 studies assessing cortisol response to the TSST demonstrated no significant differences in either pre-task or post-task cortisol levels between a mixed group of people with AN, BN or BED and HCs (Monteleone et al. 2018). However, this result cannot be considered conclusive since the meta-analysis included individuals with different ED diagnoses in a combined group. Subsequent studies have suggested reduced cortisol reactivity to acute interpersonal (Monteleone et al. 2020; Schmalbach et al. 2020) and non-interpersonal stressors (Westwater et al. 2021) in individuals with AN and those with BN. This is consistent with some previous findings (Het et al. 2015; Vaz-Leal et al. 2018), and with the allostatic load theory (McEwen and Wingfield 2003) which claims that the stress induced prolonged HPA axis activity may result in a dampened functional reactivity. However, a dampened cortisol stress reactivity can only be hypothesised to occur in AN, and further studies are needed to investigate this field.

Some research has been published reporting on the CAR in individuals with AN, but meta-analyses are lacking. Briefly, most, but not all, studies support the CAR is enhanced in underweight individuals with AN, especially in those with AN-BP, but not in weight-restored individuals with AN (Monteleone et al. 2016b; Monteleone et al. 2017). These data further support the occurrence of HPA axis hyperactivity in the acute stage of AN, although this area deserves further exploration.

Interestingly, a recent review (Rossi et al. 2024) outlined that dampened HPA basal activity (namely, 24-h urinary free cortisol levels and morning plasmatic cortisol levels) and reduced CAR and stress reactivity characterise individuals with AN and childhood maltreatment. Future studies will explore the hypothesis that HPA activity may represent a marker of early adverse experiences in individuals with AN.

To summarise, existing literature converges on the idea that HPA axis basal activity is enhanced in the acute stage of AN, which, in turn, implies increased secretion of cortisol in underweight individuals with AN. It has been proposed that such an increase in cortisol production may be a physiological adaptation to starvation and malnutrition (Fichter et al. 1986), although its state-dependent nature has to be confirmed. It is worth noting that such an increase in HPA axis activity in acute AN does not result in the usual stigmata of Cushing's syndrome, including striae, central adiposity and weight gain (Lacroix et al. 2015). Thus, elevated cortisol levels may contribute to some clinical symptoms of acute AN such as hypogonadotropic hypogonadism and low bone mineral density, since elevated cortisol interferes with osteoblast proliferation, reduces calcium absorption in the gut, decreases gonadotropin secretion and impairs the synthesis of insulin-like growth factor-1 (IGF-1), a bone anabolic factor (McCarthy et al. 1990; Canalis 1996).

3.8. Sexual and social hormones

3.8.1. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

Increased ghrelin and reduced leptin levels suppress the hypothalamic-pituitary-gonadal axis (HGA) by down-regulating gonadotropin-releasing hormone (GnRH) in the hypothalamus and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) at the pituitary level (Haines 2023). Reduction of LH and FSH leads to a reduced oestrogen production and amenorrhoea in women with AN between puberty and menopause, and delayed puberty in adolescent females with AN (Himmerich et al. 2010).

3.8.2. Dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S)

Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone – sulphate (DHEA-S), produced by the adrenal cortex, mainly serve as precursors for more potent androgens, which then exert their effects on peripheral tissues and as neurosteroids. In one meta-analysis (Thavaraputta et al. 2023), evaluating six studies including 83 individuals with AN and 76 HCs, the mean serum DHEA concentration was non-significantly higher in patients with AN compared with HCs. In a total of 15 studies with 584 individuals with AN and 251 HCs, mean serum DHEA-S was significantly lower in patients with AN vs. HCs. In another meta-analysis (Lin et al. 2022) of 15 cross-sectional studies including 1119 participants, patients with AN had significantly elevated serum DHEA levels and reduced DHEA-S levels compared with HCs. The differences between these meta-analyses in DHEA are not clear, related, perhaps, to different studies included in each meta-analysis. Due to these discrepancies, the significance of DHEA as a biomarker of AN is unclear.

In the adrenal gland, DHEA converts to DHEA-S. In the peripheral tissues, DHEA is converted to oestrogens and androgens. It is suggested that during a major physiologic stress such as AN, there is a decreased conversion of DHEA to DHEA-S and to downstream sex hormones.

A decrease in DHEA/DHEA-S levels is associated with sexual dysfunction and cognitive and mood impairment. Moreover, studies in females with AN suggest that there may be an association between low DHEA-S levels and low bone mineral density. This has led to assessment of the potential of DHEA to improve bone density in AN. The findings of these studies, including seven randomised controlled trials (RCTs) assessed in a systematic review (Lin et al. 2022), have found that, overall, DHEA does not improve bone mineral density compared with placebo after adjusting for weight gain, both as a monotherapy and when combined with oestrogen replacement. Moreover, in patients with open epiphyses, there is a risk of decreased bone mineral density and premature epiphysial closure in response to the combination therapy.

3.8.3. Sexuality, puberty, ovarian sex hormones and testosterone in AN

The main changes of sex hormones in people with AN are that the reduced production of GnRH, LH and FSH lead to decreased production of oestradiol in the ovaries in women and in the adipose tissue in men and to reduced testosterone secretion in the testes of men and the ovaries of women (Haines 2023).

Puberty is a significant risk period for development of EDs, especially in women. Recent research highlights the potential role of ovarian hormones in phenotypic and genetic risk for EDs during puberty. According to Klump (2013) both pubertal status and pubertal timing significantly increase the risk for most EDs in girls, such that advanced pubertal development and early pubertal timing are associated with increased rates of EDs. However, Castellini et al. (2016) have argued that the effect of early puberty may be less definite, as some studies indicate that early puberty increases the risk for the onset of EDs, while others have not found such an association. Nonetheless, girls who develop sexually early, are thought to be at particular risk, given that they experience pubertal-related physical changes (e.g. breast development, menarche, increased adiposity) earlier and may therefore experience more body dissatisfaction than their developmentally on-time peers.

The reduced libido of AN can be associated with both psychological mechanisms (reduced self-esteem, body dissatisfaction) and low concentrations of circulating sex hormones. Indeed, Keys et al. (1950) showed that loss of libido is a cardinal symptom of starvation. Amenorrhoea in AN is related to hypoleptinaemia-induced low concentrations gonadotrophin-releasing hormones and thus a diminished release of luteinizing hormone.

In the meta-analysis by Thavaraputta et al. (2023), which evaluated 29 studies including 1029 individuals with AN and 574 HCs, significantly lower mean serum total testosterone was found in patients with AN compared with HCs. A meta-analysis (Lin et al. 2022) of seven studies found low serum testosterone in patients with AN vs. HCs. In females, androstenedione and testosterone are produced predominantly by the adrenal and ovary. Studies have suggested a potential association in AN between low testosterone levels and both low bone mineral density and symptoms of depression and anxiety. Nonetheless, recent RCTs in women with AN have shown no improvement with testosterone replacement in bone mineral density or in symptoms of anxiety, depression, and disordered eating (Sienkiewicz et al. 2011). Interestingly, long-term treatment with metreleptin has been reported to improve bone density of lean hypoleptinaemic women (Sienkiewicz et al. 2011). A case report indicates that treatment with metreleptin might also lead to a normalisation of testosterone levels (Antel et al. 2022).

Most male patients with acute AN have low testosterone levels (Cost et al. 2020). Low testosterone levels usually normalise with weight recovery (Wabitsch et al. 2001). Therefore, there is evidence for testosterone as a state marker of AN.

3.8.4. Oxytocin

Oxytocin, a centrally secreted nonapeptide produced by the paraventricular and supraoptic nuclei in the hypothalamus, plays a critical role in facilitating social bonding (Giel et al. 2018). Oxytocin also modulates a wide range of other functions, including metabolism, stress, appetite, eating behaviour, anxiety, and depressive symptoms (Giel et al. 2018). Animal studies indicate increased oxytocin secretion suppresses appetite in both lean and obese rodents (Skinner et al. 2019). Leptin may have an impact on oxytocin secretion in rodents (Perello and Raingo 2013). Peripheral oxytocin levels in plasma, serum, and CSF have been reported to be lower in adult people with AN, although findings are inconsistent, particularly regarding plasma and CSF levels (Maguire et al. 2013). A recent meta-analysis (Ferreira and Osório 2022) assessing how peripheral oxytocin levels among patients diagnosed with various psychiatric disorders differ from HCs has supported the

presence of lower levels of oxytocin in patients with AN in comparison with HCs. A subgroup analysis in this meta-analysis revealed a more pronounced reduction in oxytocin levels among adult patients with restricting and binge-eating/purging AN subtypes. A later longitudinal study by Plessow et al. (2022) found that low basal oxytocin levels were more pronounced in AN-R compared to AN-BP These findings highlight the importance of considering AN subtype in research on oxytocin. Studies examining oxytocin levels in individuals with partially or fully weight-recovered AN have yielded mixed results (Plessow et al. 2018) showing evidence of either normal or reduced endogenous oxytocin levels. These findings leave open the question of whether 1) altered oxytocin levels reflect the acute low-weight state of AN and normalise with recovery, or 2) alterations in the oxytocin system represent a residual 'scar' from the chronic starvation or a trait of AN. Age seems to be another critical factor. Adolescents with AN exhibit a distinct mechanism, with elevated oxytocin levels in malnourished patients that persist despite partial weight recovery (Tyszkiewicz-Nwafor et al. 2020). This longitudinal study suggests the altered oxytocin levels might contribute to ongoing symptoms. It is important to note that research on adolescents with AN is still scarce.

Overall, altered oxytocin levels have been suggested as a potential biomarker of AN-R and a possible treatment target for emerging treatments for AN (Stengel and Giel 2023). However, the potential role of intranasal oxytocin administration in AN treatment remains unclear, as current research lacks conclusive evidence of its efficacy (Leppanen et al. 2017; Hasselbalch et al. 2020; Chen, Chiang, et al. 2021; Maguire et al. 2024; Ahmed et al. 2025). Intranasal oxytocin administration may hold promise as an adjunct treatment when used in conjunction with nutritional rehabilitation or psychotherapy (Miller et al. 2023) although well-controlled and larger trials are needed.

3.9. Immunological markers

3.9.1. Cytokines

As mentioned in section 3.1., GWAS and EWAS results are suggestive of a potential role of the immune system in the pathophysiology of AN. Potential additional contributors to a dysregulated immune system in AN include increased oxidative stress, chronic physiological and psychological stress, changes in the intestinal microbiota (see section 3.11.), and an abnormal bone marrow microenvironment, which lead to alterations in cytokine signalling (Gibson and Mehler 2019).

Cytokines are messenger molecules that steer, amplify or reduce an immune response. They are produced primarily by immune cells, such as B and T lymphocytes, mast cells and macrophages, but also by a range of other cells, and by microglia and astrocytes in the brain. Cytokines have a complex and extensive range of effects and operate *via* various signalling pathways. They are most commonly quantified in the serum, plasma, and cerebral spinal fluid, with bioassays such as ELISA or polymerase chain reaction (PCR) (Liu et al. 2021). Some cytokines are broadly categorised as 'pro-inflammatory' (Himmerich et al. 2019), meaning that their main or most prominent function is to upregulate the immune response (N.B. these cytokines have multifaceted effects including importance for growth processes). The release of pro-inflammatory cytokines leads to sickness symptoms (i.e. fever, malaise, loss of appetite, fatigue), which in normal circumstances is adaptive. However, a chronic or prolonged release of pro-inflammatory cytokines can have negative sequalae in the body including degenerative processes. This can also lead to neuroinflammation (inflammation of the CNS), which may occur as pro-cytokines are able to directly and quickly pass through the blood-brain barrier (Yarlagadda et al. 2009), amongst other mechanisms. The main pro-inflammatory cytokines that have been investigated in the pathophysiology of AN are tumour necrosis factor (TNF)-α, interleukin (IL)-6, and −1β, and interferon-gamma (IFN-γ) (Khairova et al. 2009; Chang and Yen 2010).

Three meta-analyses of studies comparing cytokine concentrations between people with AN and HCs have been conducted to date (Solmi et al. 2015; Dalton et al. 2018; Keeler et al. Accepted.). The earlier meta-analysis found evidence for elevated concentrations of TNF-α, IL-1β, IL-6 and TNF-receptor-II in AN, together with decreases in the IL-6 receptor (Solmi et al. 2015). Weight gain was not associated with significant changes in TNF-α, IL-6 and IL-1β, although IL-6 was no longer significantly different from HCs following weight gain (Solmi et al. 2015). Notably, shorter AN illness duration was associated with greater concentrations of IL-6. The later meta-analysis by Dalton et al. (2018) had largely similar findings, where elevations in TNF-α and IL-6 were found in AN compared with HCs, although IL-1β was not elevated.

The latest and most comprehensive meta-analysis found that only concentrations of IL-6 were higher, with a small effect size, and although TNF-α was elevated in AN, this was not the case when study outliers were removed (Keeler et al. Accepted.). Findings were

not different between AN subtypes and amongst several identified moderators including BMI and age, none were identified as significantly moderating the findings. Additionally, concentrations of IL-15 were elevated in AN compared to HCs, and levels of IL-7 were lower. Concentrations of IL-1β, IL-4, IL-8, IL-10, IFN-γ, monocyte chemoattractant protein (MCP) and transforming growth factor (TGF)-β were similar between AN and HCs. Longitudinally, normalisation over the course of weight restoration was only found for IL-6 but not TNF-α or IL-1β.

The heterogeneity across findings may be attributable to differences in methodology, sample characteristics or lifestyle factors (e.g. diet). Additionally, given EDs are a risk factor for the development of autoimmunity, and vice versa (Raevuori et al. 2014; Hedman et al. 2019; Sirufo et al. 2022) it is possible that there is a cohort of individuals with AN who present with a heightened inflammatory state. For example, one study found that despite the absence of differences between AN and HCs in IL-6 concentrations, when examining the distribution of IL-6 values, the majority of those in the highest 10% were AN cases (Nilsson et al. 2020). This finding supports the future investigation of a potential 'inflammatory subgroup' of AN.

Elevations in the pro-inflammatory cytokines TNF-α and IL-6 have been previously considered as potential biomarkers for AN, although they do not show specificity to AN as elevations are also observed in people with other psychiatric disorders such as major depressive disorder (Dowlati et al. 2010). Thus, they may be a generic marker of psychopathological severity or treatment response, although this should be explored further in well-designed studies accounting for confounding influences. Additionally, as aforementioned the presence of an inflammatory subgroup of people with AN is a possibility – a hypothesis that should be explored in studies with larger and more diverse samples. Studies with larger sample sizes and a range of cytokines and other immune cells are also warranted to investigate the possibility of dysfunctional networks between individual molecules, given the complexity of the signalling pathways, downstream effects and bidirectional influences between cytokines and their targets. There has been some discussion that reducing concentrations of pro-inflammatory cytokines might constitute a target for treatment in the future, for example with TNF-α blockers (Dalton et al. 2018). However, recommendations cannot be made given the heterogeneity of the evidence, and given that individuals with AN have a higher risk for bacterial infection (Birmingham and Treasure 2019; Keeler et al. 2023).

3.9.2. Immunoglobulins reactive with α-melanocyte-stimulating hormone (α-MSH)

As explained in section 3.4.2., α-MSH is an anorexigenic neuropeptide of the melanocortin system which plays a key role in the regulation of appetite and body weight (Anderson et al. 2016). α-MSH plasma levels are, however, highly variable, with different studies in AN reporting either lower or similar levels compared with HCs (Galusca et al. 2015; Seitz et al. 2024).

Caseinolytic protease B (ClpB), a protein produced by the Enterobacteriaceae family of gut bacteria, is an antigen-mimetic of α-MSH (Tennoune et al. 2014) which means that ClpB has structural similarity with α-MSH which is why the immune system produces antibodies that cross-react with both the bacterial protein ClpB and the endogenous appetite-reducing hormone α-MSH (Thomas et al. 2025). The relevance of α-MSH-reactive IgG to AN was first shown by positive correlations of its plasma levels with the Eating Disorder Inventory 2 (EDI-2) scores (Fetissov et al. 2005). This link appeared to be specific for α-MSH, since the same study did not find correlations for IgG reactive with other regulatory peptides such as oxytocin or corticotropin. In AN, the α-MSH IgG complexes have been suggested to lead to an increased biological activity compared to α-MSH alone by three different mechanisms: IGG antibodies act as a carrier for α-MSH and protect it from degradation by enzymes, the α-MSH IgG complexes trigger MC4R signalling at lower concentrations; and the α-MSH IgG complexes increase the rate at which the MC4R is internalised by cells which a marker of high receptor activity (Lucas et al. 2019).

Plasma levels of IgG reactive with α-MSH were therefore suggested as putative biomarkers of AN. However, no significant group differences between patients and HCs were found (Fetissov et al. 2005; Roubalova et al. 2021). Seitz et al. even reported low levels of α-MSH-reactive IgG in adolescents with AN at an early stage of disease coinciding with low total serum IgG concentration (Seitz et al. 2024). α-MSH-reactive IgG correlated positively with BMI-standard deviation score (BMI-SDS) in both patients with AN and in healthy adolescents (Seitz et al. 2024). The authors of this study discussed the high variability of α-MSH and of IgG-bound α-MSH, starvation-related downregulation of α-MSH and IgG production, counter-regulatory endocrine mechanisms, treatment effects and disease duration as potential influencing factors that might explain differences in study results (Seitz et al. 2024).

Bacterial ClpB is naturally present in the plasma of healthy subjects with levels correlating negatively

with BMI suggesting an anorexigenic effect of ClpB. Reduced immune control of ClpB due to low plasma levels of anti-ClpB IgG in patients with AN were therefore suggested to contribute to the increased anorexigenic potency of this bacterial protein and facilitation of food restriction (Thomas et al. 2025). A recent preclinical study demonstrated that immunoneutralization of ClpB prevents development of activity-based anorexia (ABA) in mice (Thomas et al. 2024).In short, the current literature contains two different hypotheses how of ClpB, α-MSH and α-MSH-/anti-ClpB reactive IgG might influence the development of AN. One hypothesis is that anti-α-MSH IgG protect α-MSH from degradation and enhance its anorexigenic signalling at the MC4R (Fetissov et al. 2005; Lucas et al. 2019). However, cross-sectional studies did not find higher anti-α-MSH IgG levels in people with AN compared to HCs (Fetissov et al. 2005; Roubalova et al. 2021; Seitz et al. 2024). A different hypothesis is that ClpB itself has anorexigenic effects and that a reduced immune control of ClpB due to low plasma levels of anti-ClpB IgG increases the anorexigenic potency of ClpB (Thomas et al. 2025).

For future studies, it has been suggested that a combined analysis of α-MSH, α-MSH- and ClpB-binding IgG and ClpB protein could elucidate the combined effects of these molecules in the pathophysiology of AN (Fetissov and Hökfelt 2019).

IgG binding ghrelin has been shown to protect this orexigenic hormone from degradation in plasma and enhance its signalling upon the ghrelin receptor (Takagi et al. 2013). Low plasma levels of ghrelin-binding IgG were found in patients with AN and were increased after refeeding (Terashi et al. 2011). It is, hence, possible that the orexigenic effect of ghrelin is attenuated in AN because of its insufficient protection by IgG.

3.9.3. Leukocytes

Leukocytopenia (a low leukocyte count) is frequently encountered in people with AN where it is seen as a sign of self-starvation induced bone marrow suppression. A recent systematic review and meta-analysis of cross-sectional studies (Keeler et al. 2025) found that concentrations of lymphocytes, basophils, monocytes and neutrophils were lower in AN than in HCs. Additionally, the leukocytopenia of AN may be associated with an increased risk of severe infectious diseases (Himmerich et al. 2010). The cytopenias of AN are thought to be secondary to starvation and bone marrow insufficiency. These changes typically resolve with nutritional rehabilitation (Cleary et al. 2010).

3.9.4. C-reactive protein

A recently published cross-sectional meta-analysis found that C-reactive protein (CRP) levels were significantly lower in people with AN compared to HCs, potentially due to malnutrition. The authors suggested that because of reduced CRP levels, patients with AN might be at risk for bacterial infections or autoimmune diseases (Xu et al. 2025).

3.10. Metabolomics

Metabolomics, the identification of small molecules known as metabolites, is a promising area to explore for potential biological abnormalities in individuals with AN (Himmerich and Treasure 2024). Techniques such as mass spectrometry and nuclear magnetic resonance spectroscopy are commonly used to quantify metabolites in human samples. This section examines how metabolomics differs between subtypes and stages of AN, and between AN and other psychiatric and metabolic disorders. A summary of studies on metabolomics in AN is presented in Table S7, and Table S8 provides a synopsis of meta-analytic results of these studies.

3.10.1. Amino acids and derivatives

Amino acids are organic compounds which are essential for the synthesis of proteins, neurotransmitters and other important nitrogen-containing compounds, such as peptide hormones. They are absorbed from the gastrointestinal tract following oral ingestion. Preliminary evidence suggests there may be altered levels of specific amino acids and their derivatives between patients with AN and HCs. Thus, reduced levels of essential amino acids for haemoglobin synthesis and energy regulation (Miyata et al. 2021; Monteleone et al. 2021b) and non-essential amino acids for protein synthesis (Miyata et al. 2021) have been found in patients with AN compared to HCs. However, findings are far from consistent and indicate the need for further study. For example, glutamate, an excitatory neurotransmitter involved in memory and mood regulation, has been observed to be reduced in faecal samples from acutely ill and recovered individuals with AN-R relative to HCs (Tomášová et al. 2022). However, in another study, no statistically significant difference in glutamate concentration in right inferior lateral prefrontal cortex and right occipital cortex was found between acute AN-BP and HCs (Westwater et al. 2022). The latter study acknowledged the potential impact of psychotropic medication on glutamate turnover.

Changes in neurotransmitter levels and metabolites following weight restoration have been observed, suggesting the importance of considering the impact of nutritional status on metabolic profiles. For example, serum level of tyrosine, a precursor for various neurotransmitters, did not differ significantly between acute AN and HCs, but was significantly raised after weight restoration (Föcker et al. 2020). The picture is further complicated when exploring AN subtypes, with faecal tyrosine level being reduced in acute AN-R but raised in acute AN-BP (Monteleone et al. 2021b) compared to HCs (Miyata et al. 2021). More studies are needed to determine the role of neurotransmitters in the biomarker profile of AN.

3.10.2. Carbohydrates

Carbohydrates play a crucial role in energy production and are the main energy source for human metabolism. However, some patients with AN avoid consuming carbohydrate containing food like bread and starchy vegetables (Buck et al. 2022) in addition to the dietary restriction, which further affects the carbohydrate-related metabolite levels and other components necessary for normal metabolism.

Considerable research indicates that glucose, carbohydrates, sugars and their derivatives are generally lower in individuals with AN compared to those who are recovered from AN and HCs (Föcker et al. 2012; Monteleone et al. 2021a; Salehi et al. 2021). The malnutrition of AN contributes to disturbances in energy metabolism which, in turn, may affect most carbohydrate metabolites, if not all. However, studies investigating this subgroup of metabolites in human samples have found inconsistent results. Some studies found varying concentrations of hexoses, fucose, rhamnose, N-acetyleglucosamine, tagatose and other types of sugars in AN while others suggested that levels may differentiate people with active AN from those with recovered AN and HCs (Monteleone et al. 2021b, 2021c). For the use of blood glucose concentration for clinical risk management, see section 3.15.3.

Sugar alcohol and its derivatives have received minimal attention in individuals with AN. Levels of scyllo-inositol and glycerol have been found to differ between AN subtypes (namely AN-R and AN-BP) and illness stages (namely acute AN, recovered AN and HCs) (Monteleone et al. 2021b). Both myo-inositol and meso-erythritol-1 were significantly reduced in patients with AN relative to HCs (Monteleone et al. 2021c; Westwater et al. 2022).

3.10.3. Lipids

Lipoproteins, saturated fatty acids, polyunsaturated fatty acids such as omega-3 and omega-6 fatty acids, short-chain fatty acids (SCFAs), carnitine derivatives might play a role as biomarkers in AN.

Lipoproteins are complex particles composed of lipids and proteins that transport lipids, like cholesterol and triglycerides, through the bloodstream. They can be measured in plasma using nuclear magnetic resonance spectroscopy. Lipoproteins have been investigated for their prognostic role in patients with AN. An increase in very low-density lipoprotein (VLDL) in childhood was associated with a lower risk of developing AN, while an increase in HDL at seven years was associated with a higher risk of developing AN at age 18 (Santos Ferreira et al. 2019). In individuals with AN, studies have found increased levels of lysophosphatidylcholine, lysophosphatidylethanolamine, phosphatidylinositol and sphingomyelin even after short term weight-restoration compared to HCs (Tam et al. 2021). Other studies have shown significant differences in lipid levels between AN and HCs, as well as between baseline and study timepoints. These lipids include glycerophspholipids, sphingolipids and lysophospholipids (Föcker et al. 2012, 2020; Tomášová et al. 2022).

Preliminary but consistent findings have been observed in the levels of saturated fatty acids in patients with AN. Faecal levels of stearic acid, lauric acid and its derivative hydroxystearic acid were all increased in patients with AN (Monteleone et al. 2021c), despite dietary restriction. The increase in saturated fatty acids remained high after weight restoration (Monteleone et al. 2021c). Additionally, when faecal levels of saturated fatty acids were tested acutely before nourishment, they remained high (Nguyen et al. 2019; Monteleone et al. 2021c). Comparisons among AN subtypes yielded consistent results, with the AN-BP subtype showing higher levels of faecal palmitic acid than the AN-R subtype (Monteleone et al. 2021b). Hussain et al. (2019) have conducted a meta-analysis finding increased concentrations of lipid metabolites in patients with acute AN and those who were partially weight restored.

Omega-3 fatty acids are polyunsaturated fatty acids that cannot be produced by the body and must therefore be obtained through diet. They are characterised by the location of their first double bond three carbons away from the methyl end of their carbon chain. Levels of docosahexaenoic acid (DHA), alpha linolenic acid (ALA), stearidonic acid (SDA), Eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA) were all

found to be elevated in patients with acute AN. Some of these omega 3 fatty acids, such as DHA, were associated with a higher risk of developing AN by the age of 18 (Shih et al. 2016; Nguyen et al. 2019; Santos Ferreira et al. 2019). Recovery from AN normalised levels of omega-3 fatty acids, including SDA (Shih et al. 2016). However, individuals with recovered AN had higher levels of omega-3 fatty acids compared to HCs, particularly DPA (Shih et al. 2016).

One study found increased levels of omega-6 fatty acids in individuals with AN in comparison to HCs. This includes gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and octadecadienoic acid (OBA) (Shih et al. 2016). When compared to those who recovered from AN, levels of OBA and SDA were higher in acute AN. Similar to omega-3 fatty acids, the comparison between recovered AN and HCs showed that recovered AN patients have higher levels of the omega-6 fatty acid, OBA (Shih et al. 2016). One study found that increased levels of the monounsaturated fatty acid (FA) ratio at age seven years were associated with a lower risk of developing AN at age 18 (Santos Ferreira et al. 2019).

SCFAs have been found to be higher in acute AN (Monteleone et al. 2021a). A recent study found that valeric acid was the only SCFA associated with BMI (Castellini et al. 2023). Similar to most fatty acid findings, faecal levels of valeric and propionic acid were increased in individuals with AN, which remained high even after weight restoration (Monteleone et al. 2021c). On the contrary, acetate, butyric, isobutyric and isovaleric acids were significantly lower in acute AN and people who recovered from AN (Monteleone et al. 2021c; Xu et al. 2022). After nourishment, acetate and propionic acid were lower in AN (Prochazkova et al. 2021). Additionally, studies have shown that SCFAs and BMI were significantly correlated, suggesting a crucial role of SCFAs in weight management (Xu et al. 2022). See also paragraph 3.11.1.1. on SCFAs as microbial metabolites.

Carnitine derivatives are crucial molecules involved in the beta-oxidation process of fatty acid metabolism. These molecules are sensitive to nourishment states. Studies have found reduced concentrations of butyrylcarnitine, O-acetylcarnitine, octanoylcarnitine, acetyl-L-carnitine and palmitoylcarnitine in people with acute AN (Föcker et al. 2012; Miyata et al. 2021).

Research has linked these disturbed metabolomic profiles with extreme low intake of calories, which could be partially modified after nourishment. Therefore, it might be premature to draw a conclusion on whether the use of this category of metabolites is helpful as a biomarker for patients with AN. However, meta-analytical evidence shows increased levels of total cholesterol, HDL, low density lipoprotein (LDL), triglycerides and free fatty acids in patients with acute AN compared to HCs (Hussain et al. 2019). These changes remain after weight restoration which suggests a persistence of metabolic dysregulation after weight restoration (Hussain et al. 2024).

3.10.4. Vitamins and coenzymes

A few studies have examined vitamins and coenzymes in people with AN. Increased levels of choline (B4) were reported in 10 patients with acute AN, compared to HCs (Miyata et al. 2021). In addition, increased total concentration of choline in GM has been reported in 30 predominantly adolescent patients with AN, compared to age-matched female HCs (Doose et al. 2023), indicating lipid catabolism. No significant difference in Cobalamin (B12) was noted between AN-subtypes, although lower BMI was associated with higher level of cobalamin (B12) in acute phase of illness (Burdo et al. 2020). Small sample sizes and multiple testing render it difficult for a firm conclusion to be drawn. The former concern was raised by one study regarding the finding of raised folate (B9) in 53 patients with acute AN and 40 patients in remission from AN, compared to 36 HCs (Burdo et al. 2020). Lower levels of nicotinamide (B3) and nicotinate (Vitamin E) have been reported in faecal samples of patients with AN compared to HCs, but the difference in nicotinamide (B3) became statistically insignificant following refeeding (Tomášová et al. 2022).

3.10.5. Steroids

Steroids are hormones that are made naturally in the human body and that are chemically characterised by four fused carbon atom rings. Cholesterol is the precursor molecule to many steroid hormones, including sex hormones and hormones necessary for metabolism, water and electrolyte balance in the body.

The acute phase of AN is associated with a disruption of steroid metabolism. Compared to HCs, people with acute AN show higher concentrations of cholesterol and other metabolites of the lecithin-cholesterol acyl transferase (LCAT) pathway that persist after a short-term weight restoration refeeding program (Tam et al. 2021). The effect of refeeding on steroid metabolism in people with AN has been also investigated by Bulant et al. (2020) who showed that, after treatment, plasma levels of pregnenolone sulphate and 20α-dehydropregnenolone sulphate increased, whereas 7β-hydroxy-DHEA, 5-androstene-3β,7β,17βtriol, epipregnanolone, and epietiocholanolone levels significantly decreased. Notably, higher DHEAS

blood levels in people with AN predicted weight gain at 3- and 6-months and increase in fat mass and appendicular lean mass (Kimball et al. 2022) Increased serum levels of cholesterol typically occurring in the acute phase of AN could also explain the enhanced concentrations of faecal coprosterol (or coprostanol) of patient with AN, since coprosterol is a cholesterol derivative formed from the biohydrogenation of cholesterol in the gut likely by intestinal bacterial flora (Monteleone et al. 2021c). The pathophysiology of increased cholesterol concentration in the blood of people with AN is still not fully understood. People with AN often show decreased blood levels of the thyroid hormone triiodothyronine (T3). T3 regulates the cholesterol ester transfer protein (CETP) which affects cholesterol metabolism. People with AN have been reported to have increased CETP activity and, therefore, increased cholesterol (Ohwada et al. 2006).

3.10.6. Organic acids

Organic acids are organic compounds with acidic properties such as carboxylic, sulphonic lactic and pyruvic acid. Some short organic acids are important metabolites produced by the gut microbiome. Therefore, additional information on these specific organic acids is available in section 3.11. of this article.

Increased lactate and pyruvate serum concentrations have been found in acute and recovered patients with AN (Salehi et al. 2021; Tomášová et al. 2022). These metabolites are involved in metabolic pathways such as glycolysis and gluconeogenesis, providing energy under aerobic and anaerobic conditions. Concentrations of branched-chain keto acids have been found to be lower in serum of people with acute AN compared to HCs (Tomášová et al. 2022), while higher in faecal samples, persisting after weight restoration (Monteleone et al. 2021a). Since branched-chain keto acids inhibit glucose production in hepatocytes suppressing liver mitochondrial pyruvate carrier activity and pyruvate-supported respiration (Nishi et al. 2023), it has been hypothesised that, in addition to being linked to the state of emaciation, lower circulating levels of branched-chain keto acids may constitute a compensatory mechanism to maintain pyruvate-/lactate-driven glucose production.

Concentrations of several other organic acids (such as succinate, malate, fumarate and citrate) have been found, even if not consistently, reduced in serum and stool samples from people with AN compared with HCs (Miyata et al. 2021; Salehi et al. 2021; Tomášová et al. 2022). A preliminary study showed that faecal concentration of acetic, succinic, malic, sebacic and p-hydroxyphenylacetic acid differed between AN-R and AN-BP. Indeed, compared to HCs, p-hydroxyphenylacetic, acetic and succinic acid were higher in AN-BP and lower in AN-R, while malic acid concentration was lower in AN-R and AN-BP (Monteleone et al. 2021b).

Serum levels of uraemic toxin-related compounds p-cresyl sulphate, indole-3-acetic acid and phenylacetic acid were found to be higher in acute AN than HCs (Miyata et al. 2021). Moreover, concentrations of p-cresyl sulphate were positively associated with abundance of *Clostridium coccoides* group and *Clostridium leptum* subgroup in people with AN, suggesting that changes in uraemic toxins are potentially linked to the gut dysbiosis occurring in acute AN. Lower serum methanol concentration in acute and weight-restored AN compared with HCs has also been associated with altered microbiome metabolism due to lower gut microbiota diversity (Salehi et al. 2021).

In summary, tentative evidence suggests a potential role of metabolomics in understanding the metabolic disturbances associated with AN. Patients with AN may exhibit distinct metabolic differences compared to HCs. Understanding these differences between AN-subtypes and stages of illness can provide important insights into the underlying mechanisms and inform the development of potential therapeutic interventions for AN.

3.11. Microbiome and markers of the gut-brain-axis

In patients with AN, perturbations in gut microbiota composition have been reported to be associated with gastrointestinal (GI) symptoms (Riedlinger et al. 2020; Di Lodovico et al. 2021; Anton-Păduraru et al. 2023; Garcia and Gutierrez 2023). For instance, constipation emerges as a prevalent issue in AN, attributable to enduring food restriction. Similarly, patients with AN frequently report sensations of abdominal fullness, which are often cited as a reason for food refusal. Interestingly, this symptomatology aligns with objectively assessed delays in gastric emptying time, a phenomenon that tends to ameliorate during the refeeding process. During the process of refeeding and rehabilitation, involving normalisation of eating patterns and/or attaining a healthy body weight where applicable, a notable transformation in GI symptoms unfolds. This metamorphosis entails the persistence of certain complaints, the disappearance of others, and the emergence of new ones (Riedlinger et al. 2020; Riedlinger et al. 2022). Notably, overall improvement in lower GI symptoms surpasses that observed in the upper GI tract throughout refeeding (Riedlinger et al. 2020; Riedlinger et al. 2022).

GI symptoms, such as constipation, intertwined with disordered eating patterns and aberrant food intake behaviours, potentially compounded by compensatory measures like vomiting or laxative abuse, may contribute to a distinct microbial environment within the colon compared to individuals with healthy GI function (Mack et al. 2018). Consequently, it is not surprising that GI microbiota composition between individuals with AN and their healthy counterparts is often different, as highlighted by recent reviews (Di Lodovico et al. 2021; Nikolova et al. 2021; Anton-Păduraru et al. 2023; Garcia and Gutierrez 2023).

Human studies analysing the GI microbiota in AN cross-sectionally compared to HCs and/or longitudinally are listed in Table S9. The microbiome is typically characterised by its richness, diversity, and community structure. Richness represents a simple census of the unique species present within a sample, independent of their individual population sizes. Diversity is categorised into two primary scales: α-diversity, which measures the variety of species or strains within a single sample, and β-diversity, which quantifies the variation in microbial composition between different samples or over time. The community structure dictates the microbiome's functional capacity. Even if two microbial communities share the same total bacterial count, differences in their structural organisation will lead to distinct outcomes in nutrient metabolism, pathogen defence, and vitamin synthesis. A structure characterised by high diversity and evenness is generally more resilient, possessing a superior ability to recover its functional equilibrium following a disturbance, such as a course of antibiotics (Qian et al. 2020).

When comparing AN with HCs, eight studies reported no difference, three studies showed a decrease, and one study showed an increase in microbial richness, whereas in five studies, this was not reported or was not applicable. Similarly, regarding microbial diversity, 11 studies reported no difference, one study a decrease and five studies did not assess microbial diversity when comparing patients with AN and HCs. However, regarding the microbial community structure, differences were observed in 10 studies, no differences in two and in five studies, the microbial community structure was not assessed. Thus, α-diversity appears unaffected, but differences in the microbial community structure are likely. There is only one meta-analysis that was able to pool the data from four studies, which is why conclusions can hardly be drawn. It found a slight increase in α-diversity in AN versus HCs but comparable β-diversity (Di Lodovico et al. 2021). However, most studies report inconsistent changes in certain taxa. Nevertheless, there may be tendencies towards a reduction in butyrate-producing species and an increase in mucin-degrading species (Di Lodovico et al. 2021).

There are some indications that gut microbiota composition in acute AN may contribute to maintaining low weight or continued weight loss. Fan et al. (2023) showed that faecal transplantation from patients with AN into a classical model of germ-free mice led to reduced weight gain compared to mice receiving faecal transplants from healthy, normal-weight donors when combined with food restriction (Fan et al. 2023). They also found hypothalamic gene expression of anorexigenic genes like BDNF to be increased and that of orexigenic genes like ghrelin to be reduced, potentially explaining their findings. These results corroborate findings from an earlier study, where mothers of mice pups received faecal transplants from healthy donors and patients with AN. The pups of AN-transplanted mothers had reduced weight gain, decreased appetite and reduced energy efficiency as well as increased anxiety and obsessive-compulsive traits (Hata et al. 2019).

However, Glenny et al. (2021) performed faecal microbiota transplants into germ-free mice with ad libitum access to food and water. The mice were colonised with samples from three distinct donor groups: patients with AN prior to treatment, the same patients following renourishment, and age- and sex-matched HCs. Despite the different origins of the microbiota, the mice receiving AN-derived samples exhibited no significant differences in body weight compared to those receiving HC samples; after four weeks, body weights across all groups remained comparable (Glenny et al. (2021). A detailed overview of studies analysing gut microbiota before and after weight rehabilitation in human AN is displayed in Table S8. For both microbial richness and community structure, study findings were inconsistent, whereas findings were consistent for microbial β-diversity which remained stable within the individuals across time, if reported.

Studies including adolescents or children with AN are still in the minority (Andreani et al. 2024) and their results remain difficult to interpret. However, research this early in the disease course might be an essential step to help discern the chicken-and-egg question of causality regarding the microbiome-gut-brain axis in patients with AN.

Gut microbiota in AN may affect psychological processes *via* the gut-brain-axis. Kleiman et al. (2015) found a negative link between depression levels and microbial richness, contrasting with the observations

of Schulz et al. (2021) of no correlation between bacterial richness/diversity and depression/anxiety symptoms. Borgo et al. (2017) noted a negative relationship between depression scores and *Clostridium* species as well as between faecal butyrate concentrations and symptoms of depressive/anxiety disorders. Similarly, Castellini et al. (2023) identified a connection between the bacterial community, butyric acid, and anxiety in patients with AN. However, the above studies had small sample sizes. Fan et al. (2023) discerned numerous further associations, including 11 taxa with EDI-3 related ED symptoms and seven taxa with BMI. The degree of depression symptoms was not explanatory for the microbiota composition in a large cohort of adolescents and young adults (Andreani et al. 2024).

Notably, most studies highlighted a significant correlation between depression (Borgo et al. 2017) and anxiety (Borgo et al. 2017; Castellini et al. 2023) and BMI in their cohorts. A detailed investigation and the only study consequently controlling for patients BMI was a re-analysis of the MICROBIAN study (Mack et al. 2016) conducted by Ketel et al. (Ketel et al. 2024). Several significant associations between psychological parameters and gastrointestinal microbiota were attenuated after controlling for patients' BMI. Post-rehabilitation, positive links were noted between species of *Blautia* and *Ruminococcus* and depressive symptoms. Additionally, during inpatient treatment, propionate and acetate levels exhibited a positive correlation with reductions in depression severity (Ketel et al. 2024). Overall, the situation is unclear.

3.11.1. Microbial metabolites

Although composition of gut microbiota in patients with AN varies across studies, a common factor could be the metabolic potential of the microbiome. More important than the presence of specific bacteria seems to be the molecules that the microorganisms produce and with which they can affect the physiology of their host.

3.11.1.1. Short-chain fatty acids. Several studies examining gut microbiome composition of patients with AN have shown a lower proportion of bacteria producing SCFAs, mainly acetate, propionate, and butyrate, compared to HCs (Morita et al. 2015; Borgo et al. 2017; Prochazkova et al. 2021). These molecules are mainly produced by microbial fermentation of dietary fibre. SCFAs are an important source of energy for colonocytes, as well as for distant organs such as liver, muscles and brain. In addition, they play an important role in gut-brain signalling, including influencing the expression of peripheral appetite-regulating peptides such as PYY and GLP-1 by enteroendocrine L cells *via* the GPR41 and GPR43 (Chambers et al. 2015; Yu et al. 2024). SCFAs can also regulate leptin levels by activating the free fatty acid binding receptors (FFARs) in adipocytes (Gabriel and Fantuzzi 2019). At the same time, SCFAs modulate the production of central appetite-regulating peptides in the hypothalamus, such as the orexigenic NPY and AgRP or the anorexigenic POMC (Roubalová et al. 2024; Yu et al. 2024).

SCFAs are also important modulators of immune response that regulate mucosal barrier integrity, mucosal immunity and susceptibility to intestinal immune disorders. They signal to cells *via* GPRs expressed on immune cells such as neutrophils, macrophages, dendritic cells and lymphocytes in the gut. Butyrate and propionate can also get into cells by passive diffusion and affect gene expression by inhibition of histone deacetylase. In the gut, SCFAs affect different pathways such as the NF-κB signalling pathway that mediates transcription of various cytokines and chemokines, e.g. IL-1β, TNF-α, IL-2 (Liu et al. 2023). Recent meta-analyses suggest AN may be associated with elevated levels the proinflammatory cytokines IL-1β, TNF-α, and IL-6 (Solmi et al. 2015; Dalton et al. 2018). Thus, in patients with AN, decreased levels of SCFA-producing gut bacteria may contribute to a shift in the immune response towards a pro-inflammatory state and an increased risk of immune-mediated inflammatory diseases such as type 1 diabetes, rheumatoid arthritis and inflammatory-bowel disease (IBD) (Mann et al. 2024). A Danish population-based study found that a prior AN diagnosis was associated with the development of IBD later in life (although the reverse was not observed) (Larsen et al. 2021). Therefore, the therapeutic potential of SCFAs is now being explored.

3.11.1.2. Neurotransmitters. Multiple neurotransmitters are secreted by the gut microbiome. They can affect metabolism, appetite, immunity, and anxiety and stress behaviour (Neuman et al. 2015). In some studies, faecal levels of neurotransmitters serotonin, dopamine, and GABA were decreased in patients with AN compared to HCs (Prochazkova et al. 2021). Microorganisms not only produce neurotransmitters but also influence their synthesis *via* enteroendocrine cells of the intestine. In addition, their metabolic activity can reduce the bioavailability of their precursors such as tryptophan, tyrosine or glutamine ingested with food. Several studies showed a higher abundance of bacterial genus Alistipes in patients with AN compared to HCs (Di Lodovico et al. 2021). Members of this genus can hydrolyse serotonin precursor tryptophan to indole and thus decrease serotonin bioavailability and may be involved in anxiety and depression. Animal studies using the ABA model have shown that dysregulation

of the GABAergic system, particularly involving $GABA_A$ receptors, is associated with anxiety-like behaviour and reduced food intake. Also, modulation of hypothalamic GABAergic signalling has been shown to enhance food intake in rodents (Spadini et al. 2021). Further, evidence points to alterations in dopamine levels and signalling in individuals with AN. Specifically, functional MRI studies have observed altered activation in brain regions associated with reward processing, suggesting a dysfunctional striatal dopamine system in AN (Gorwood et al. 2016).

3.11.1.3. Bile acids. Bile acids can significantly influence the composition and function of the microbial community through their antimicrobial properties. At the same time, bacteria encode many enzymes that can metabolise these acids and change their composition. This microbial manipulation of the bile acid pool contributes to the maintenance of intestinal homeostasis, while imbalances in this system are associated with various diseases. Studies using metabolomics profiling showed higher concentrations of both primary and secondary bile acids in the serum of patients with AN compared to HCs (Perino et al. 2021; Fan et al. 2023).

3.11.2. Manipulation of the gut microbiota

Interest in employing therapeutics targeting the gut microbiota in AN stems in part from the association of AN with GI and weight issues. Currently, treatment with probiotics (Solis et al. 2002; Nova et al. 2006; Žaja et al. 2021) or parabiotics/postbiotics (inactivated bacteria or fractions) and stool transplantation (faecal microbiota transplantation; FMT) (Aira et al. 2020; Wilson et al. 2023) are undergoing study (Socała et al. 2021).

FMT may be a complementary treatment strategy for AN. The introduction of FMT from a healthy donor may help to restore the integrity of the intestinal barrier, support immune homeostasis and improve the regulation of satiety and hunger. A recent study showed a weight gain of 13.8% over a 36-week period in patients with AN diagnosed two years prior to FMT (de Clercq et al. 2019). Another study explored changes in the gut microbiome, microbial metabolites and clinical parameters in patient with severe and enduring AN and small intestinal bacterial overgrowth syndrome (SIBO). Post-treatment analyses showed an improvement in gut barrier function, increased bacterial diversity, and elevated levels of SCFAs. However, no significant clinical improvement in AN symptoms was observed (Prochazkova et al. 2019). The results of the studies suggest that earlier intervention might be more beneficial for patients with AN.

The effect of probiotic or prebiotic supplementation was determined in several studies. A recent case-control study involving 100 children with AN demonstrated beneficial effects of a four-strain probiotic supplementation, including improved gut-brain communication, restoration of the gut microbiome, and enhanced clinical outcomes (Lu et al. 2025). In another randomised, placebo-controlled study, 31 female paediatric patients with AN and constipation received 10^8 CFU of *L. reuteri* DSM17938 per dose for 3 months. The probiotic supplementation resulted in improved gastrointestinal motility and weight restoration (Žaja et al. 2021).

3.12. Salivary markers

Saliva is a valuable but underused matrix in human biomonitoring. By focusing on this accessible and clinically relevant fluid, new tools for early health risk assessment and non-invasive diagnostics can be obtained. From the oral perspective AN impact on salivary biomarkers is linked to hyposalivation, inflammation, oxidative stress, and microbiota disruption. A general meta-analysis and separate studies have shown decreased salivary pH (MD ≈ −0.39) and salivary flow (MD ≈ −0.27 ml/min) in AN patients. In a retrospective study, patients with AN were affected by higher levels of albumin, inorganic phosphate, aspartate aminotransferase (ASAT), chloride, magnesium, and total protein. ASAT and total protein were found to be good predictors of AN disease (sensitivity approximately 65%, specificity approximately 67%) (Niederau et al. 2025).

3.12.1. Salivary microbiota

The relationship between oral microbiota and purging behaviours (such as self-induced vomiting) is an emerging area of research with increasing clinical relevance. Purging – especially vomiting – can significantly alter the oral environment, which in turn affects the microbiota. In a recent case-control study in patients with purging subtype of AN, BN or another specified ED vs. participants without EDs or any type of purging behaviour (Diaz-Perdigones et al. Submitted) oral microbiota populations between vomiting and control groups differed. *Actinomyces* and *Bulleidia* were more abundant in the vomiting group, while *Veillonella* and *Oribacterium* were less abundant compared to the control group. More importantly, vomiting frequency was related to *Actinomyces* and *Bulleidia* abundance; the more vomiting behaviour, the more *Actinomyces* and *Bulleidia* abundance, establishing these bacteria as possible markers of vomiting behaviour. However,

there is a paucity of literature on this topic and further evidence is needed.

3.12.2. Salivary HPA-axis markers

One hypothesis of the pathogenesis of AN considers altered functioning of the HPA axis (see section 3.7), autonomic nervous system (ANS) and immune system due to chronic mental stress. Biological markers in saliva available for measuring alterations of this system include alpha amylase, salivary immunoglobulin A (sIgA), cortisol and opiorphin. These stress markers can be measured in saliva where their levels correspond with plasma levels (Kirschbaum and Hellhammer 1989). Depending on their molecular weight there are three pathways that systemic constituents may pass from blood vessels to salivary gland epithelium: passing through the space between the salivary acinar cells, filtration through pores of the cell membranes or selected transport across the cell membrane (Špilak et al. 2025).

3.12.2.1. Salivary alpha amylase. Alpha-amylase in saliva (salivary alpha-amylase, SAA) is produced by the parotid gland and regulated by sympathetic nervous system (SNS). It can be used as an indicator of SNS activity and peripheral marker of central norepinephrine release. SAA level depends on the function of the parotid glands, presence of carbohydrates in food and time of day. Levels of SAA decrease after waking up and then slowly increase with a peak in the late afternoon and evening.

Hypercortisolaemia due to prolonged mental stress can lead to the alterations in SAA levels. Based on this finding it was suggested that both restrictive and binge-purging types of AN may lead to increase of SAA activity. Cross-sectional case-control studies of restrictive AN failed to show any alterations in the level of SAA compared to HCs (Paszynska et al. 2016, 2020b). However, there was no comparison with other AN subtypes, weight-restored AN individuals or 24-h measurement protocols (Paszynska et al. 2016, 2020b). A recently published meta-analysis of SAA levels showed that the mean difference between AN patients and controls was +6.32 units per litre (U/l), yet it was not statistically significant ($p = 0.32$), (Niederau et al. 2025). Under conditions of stress, SAA secretion may have additional peaks that suggests an asymmetry between HPA axis and SNS as an occurrence of HPA axis hyperactivity (Paszynska et al. 2022).

All available studies on SAA in AN have a cross-sectional approach, assessing patients at a specific point in time (e.g. during hospitalisation), without further monitoring of treatment effects.

3.12.2.2. Secretory IgA. Immunoglobulins (IgA, IgG, IgM) in saliva are auto-antibodies of regulatory peptides, significant anti-inflammatory factors and their role is not limited only to protection against infections. Stress can influence the levels of immunoglobulins in different manners. For example, chronic academic stress, passive coping, and feelings of disgust have been reported to reduce sIgA levels, while acute academic and naturalistic stress have been found to increase sIgA production (Brandtzaeg 2007). SIgA is the major secretory immunoglobulin present on the oral mucosa. The level of sIgA in saliva correlates positively with the plasma cortisol level and fluctuates synchronously over 24 h (Hucklebridge et al. 1998). It has been shown that the sIgA concentration is related to the degree of stress and can be used for the assessment of HPA axis function (Brandtzaeg 2007). SIgA activity may influence appetite and lead to decreased food intake (Acres et al. 2012). Cross-sectional case-control studies of individuals with restrictive acute AN revealed significantly higher sIgA levels compared to HCs. Furthermore, a significant positive correlation between sIgA and cortisol concentrations was observed within the AN group. (Paszynska et al. 2016, 2020b).

It can be assumed that patients with AN often experience chronic inflammation, discomfort, decreased salivary flow and composition, as well as increased bacterial colonisation due to poor oral hygiene. These factors might lead to microinflammation and stress, which can increase the secretion of immunoglobulins in the oral cavity which might also reflect an immune system dysfunction in AN patients.

3.12.2.3. Salivary cortisol. Cortisol reflects HPA axis reactivity and in AN has been measured in various ways including free cortisol levels in saliva (Paszynska et al. 2016, 2020b; Westwater et al. 2021).Meta-analyses of studies performed among people with AN indicated higher morning serum, urine, and salivary cortisol levels than HCs (Monteleone et al. 2018; Bailly et al. 2021b; Thavaraputta et al. 2023). Interestingly, increased cortisol levels in underweight patients with AN normalise after weight gain (Lo Sauro et al. 2008; Culbert et al. 2016).Given this preliminary evidence, it can be argued that hypercortisolism in individuals with acute AN is a phenomenon mediated by the effects of starvation or malnutrition on the HPA axis *via* increased release of CRH (Gold et al. 1986). HPA axis function in individuals who have recovered from AN is still inadequate. Repeated saliva collection can be used to assess free cortisol and SAA over a long period of time.

3.12.2.4. Salivary opiorphin. Opiorphin is a salivary peptide produced by the submandibular glands that

possesses analgesic and antidepressant properties. Its biological action relates to the longer bioavailability of enkephalins and activation of μ- and δ-opioid receptors (Javelot et al. 2010; Yang et al. 2011). A case-control study did not find significant differences in opiorphin levels between patients with AN and HCs (Paszynska et al. 2020a). However, Paszynska et al. (2020b) suggested that level of salivary opiorphin may correlate with levels of stress biomarkers in AN and therefore its measurement could be used as a non-invasive method of disease assessment. The case control study of restrictive acute AN patients noted variability in opiorphin levels and lack of relationship with basic stress biomarkers (cortisol, SAA, sIgA). Opiorphin was associated with AN disease duration, Beck Depression Inventory (BDI) score, low body weight, and dental biofilm accumulation. These findings suggest that opiorphin might be a useful biomarker in monitoring of AN disease with severe malnutrition and also reflect immune conditions and inflammation (Paszynska et al. 2020b). Despite knowledge of salivary opiorphin's physiological properties its role in AN remains unexplored. There is still a lack of longitudinal and before-after weight restoration studies, and more research is needed on this topic.

3.13. Neurophysiological markers

3.13.1. Square wave jerks

Square wave jerks (SWJs) are involuntary saccades away and back to fixation. They have been observed to occur at abnormally high rates in many neurodegenerative and some psychiatric disorders. In a cross-sectional study of 23 female participants with AN and 22 matched HCs, people with AN exhibited SWJs at a significantly higher rate than HCs (Phillipou et al. 2014). The study authors suggested these findings were due to underlying changes in the GABA system.

3.13.2. Electroencephalography and nerve conduction velocity

Electroencephalography (EEG) measures electrical activity of the brain's cortex, thus enabling testing of various brain functions. The starvation of people with AN affects the brain, producing distorted thinking and a particular neurocognitive profile (Berchio et al. 2022). Testing can be performed in resting state or under certain emotional stimuli or cognitive tasks – both of which have been carried out in small studies of AN, usually involving 10-30 participants (see Tables S10 and S11). Studies have described differences in resting state EEG between AN and control participants, with microstates – which are spatial patterns of electrical voltage that remain relatively stable for short periods – in AN that are associated with internal/external signal processing (Berchio et al. 2024) and repeatedly abnormalities in posterior theta power, reflecting reduced top-down control. Evoked potential studies have yielded findings suggestive of specific patterns of information processing in AN (Karavia et al. 2024), altered attention level and attention bias to food cues, negative emotion and facial expressions (Wolz et al. 2015; Susta et al. 2022; Eichin et al. 2023), as well as a possible atypical neural mechanism underlying changes in cognitive flexibility (Berchio et al. 2023). The overall paucity of studies, with different tasks involved, different EEG measure parameters taken for analysis and various analysis methods precludes drawing robust conclusions regarding the patters described.

If epileptic seizures occur in a person with AN, they can be a consequence of starvation and electrolyte disturbances (e.g. hyponatraemia, hypomagnesemia), dehydration, hypoglycaemia, refeeding syndrome, the use of alcohol, drugs or medications that have been prescribed to treat comorbid health problems such as depression or taken without prescription to lose weight (e.g. bupropion) (Gibson et al. 2023; Himmerich and Treasure 2024). EEG signs of epileptic seizures include spikes, sharp waves, and spike-and-wave patterns.

3.14. Digital biomarkers

The intersection of digital technology and healthcare has elicited hopes for new avenues for managing complex health conditions like AN (see Table S12). Digital biomarkers have emerged as a promising area of research and development which may lead to novel insights into the diagnosis, monitoring, and management of AN which has traditionally been assessed and monitored through clinical interviews, physical examinations, and psychological assessments.

Wearable inertial sensors, such as accelerometers and actigraphy devices, have emerged as tools for objectively quantifying human motion and physical activity (PA) (O'Neil et al. 2016). These devices operate by capturing acceleration data, which can then be processed to derive a variety of PA metrics. They provide date-time stamped information regarding body acceleration, enabling real-time estimations of PA frequency, intensity, and duration with minimal burden on participants (O'Neil et al. 2016). Widely utilised research-grade devices include ActiGraph models (e.g. GT9X Link, GT3X) and Actiheart, with ActiGraph often considered a 'gold standard' for validating other consumer-based activity monitors (O'Neil et al. 2016; Suau et al. 2024).

The measurement capabilities of these devices are extensive, encompassing various aspects of physical activity and sleep. They can accurately assess step counts, estimate energy expenditure in kilocalories, and quantify time spent across different PA intensities, including sedentary, very light, light, moderate, and vigorous activity (Alberti et al. 2013; Karr 2017; Lehmann et al. 2018; Suau et al. 2024). Actigraphy appears well-suited for measuring sleep patterns, offering insights into sleep fragmentation, sleep efficiency, and napping sessions (Lim et al. 2023).

A significant advantage of objective assessment methods is their ability to overcome the inherent limitations of subjective self-report tools, such as questionnaires like the International Physical Activity Questionnaire (IPAQ) (Alberti et al. 2013; Lehmann et al. 2018). Research indicates that subjective methods frequently overestimate PA in patient populations, including those with AN, when compared to objective measurements (Alberti et al. 2013; Lehmann et al. 2018). This discrepancy underscores a crucial point: for a condition like AN, where distorted body perception and denial are core symptoms, self-report can be unreliable for behaviours such as physical activity. Therefore, objective measures from accelerometers and actigraphy become not merely supplementary but fundamental for accurate assessment of PA patterns, energy expenditure, and sleep, providing a more accurate representation of a patient's behaviour. This capability makes these devices invaluable for both clinical assessment and research in the future, as they bypass the cognitive biases often present in self-reported data.

Effective utilisation of these devices requires careful consideration of several factors. Device placement on the body (e.g. wrist, ankle, hip, or chest) can influence the validity and accuracy of measurements (Alberti et al. 2013; Karr 2017; O'Neil et al. 2016; Suau et al. 2024). Furthermore, the validity and accuracy of data can be affected by factors such as gait speed, the specific filtering processes applied during data analysis, and the monitoring conditions (e.g. controlled laboratory settings versus free-living environments) (Suau et al. 2024).

Altered physical activity and sleep disturbances are clinically significant features of AN. Excessive physical activity, often described as 'driven exercise', is a common compensatory behaviour reported in 30-80% of AN patients (Karr 2017; Lehmann et al. 2018). This elevated activity is associated with a longer duration of inpatient treatment, higher rates of chronic illness outcomes, and increased risk of treatment dropout (Lehmann et al. 2018). Beyond physical activity, individuals with EDs, including AN, commonly report poorer sleep quality (Lim et al. 2023). Specific sleep disturbances identified in AN patients include insomnia, sleep fragmentation, low sleep efficiency, and an increased propensity for napping (Lim et al. 2023). Interestingly, AN has also been linked to an 'early riser' chronotype and an elevated risk of insomnia, which contrasts with the evening-based patterns often seen in many other psychiatric conditions like mood disorders or schizophrenia (Wilcox et al. 2024).

3.14.1. Actigraphy in physical activity monitoring

Recent research has highlighted the critical role of physical activity patterns in individuals with AN. Lehmann et al. (2018) employed the SenseWear™ armband to objectively assess physical activity levels in hospitalised AN patients compared to HCs. They found that AN patients engaged more in very light and light-intensity activities while exhibiting less moderate to vigorous activities (Lehmann et al. 2018).Grosser et al. (2020) explored the association between physical activity, nutritional status, and psychological parameters in AN patients, and found an inverse relationship between time spent in sedentary behaviour and BMI outcomes (Grosser et al. 2020). Similarly, Langlet et al. (2021) quantified physical activity and sleeping behaviour during the initial week of inpatient care for AN, uncovering a significant amount of time spent inactive and variations in sleep quality among patients (Grosser et al. 2020). In another study, Sauchelli et al. (2015) used actigraphy to monitor physical and sleep activity with the Actiwatch. Although AN patients and HCs did not differ in mean time spent in moderate-to-vigorous physical activity (MVPA), fewer AN patients had a high physical activity profile compared to HCs. Both lower levels of MVPA and greater ED severity had a direct effect on poor treatment outcome. The poor physical condition of the patients during the evaluation and the restrictions of movement during inpatient and/or day hospital treatment may be attributed to the contradictory results obtained in the literature. These studies underscore the altered physical activity patterns in AN, suggesting a nuanced approach to integrating physical activity monitoring into treatment plans.

3.14.2. Smartwatch and smartphone applications in psychological response monitoring

The evolution of smartwatches and smartphones has enabled real-time monitoring of psychological responses, offering a promising tool for managing AN. Vinusha et al. (2023) developed a smartwatch with features for monitoring heart rate, finger movements, and

emotional states, aimed at assisting individuals with EDs in their recovery journey. This innovation facilitates timely interventions by alerting healthcare providers based on predetermined thresholds of heart rate changes. Additionally, the integration of a metaverse platform allows for virtual engagement between patients and caregivers, enhancing the support system available for recovery (Vinusha et al. 2023).

Complementing smartwatch innovations, smartphone applications have been developed to facilitate self-monitoring and engagement among individuals with AN. Tregarthen et al. (2015) introduced a smartphone app enabling users to self-monitor meals, emotions, behaviours, and thoughts, reaching over 100,000 users within two years. This app demonstrated the potential to engage underserved populations not receiving clinical treatment (Tregarthen et al. 2015). Keshen et al. (2020) compared electronic self-monitoring *via* Recovery Record to traditional paper records, although finding no significant differences in effectiveness, highlighted the varying preferences and contexts in which digital tools may serve as adjunct or alternative monitoring methods (Keshen et al. 2020).

3.14.3. Sensing technologies for comprehensive healthcare

The application of sensing technologies, inspired by the Interpersonal Neurobiology Theory (IPNB), promises a holistic approach to healthcare for individuals with AN. Almenara et al. (2022) suggested an approach using various sensors, including body, sociometric, and ambient sensors, to evaluate bodily processes, social interactions, and environmental influences. This comprehensive monitoring has been suggested to be able to provide deeper insights into the physiological, psychological, and environmental factors impacting AN, advocating for smarter healthcare solutions that consider the complex interplay of these elements (Almenara et al. 2022).

3.14.4. Smartphone-based ecological momentary assessment (EMA)

Several studies have utilised smartphone-based ecological momentary assessment (EMA) to investigate the dynamic interplay of affect and behaviour in AN. Kolar et al. (2016) conducted an EMA study using smartphones with 20 female adolescents with AN and 20 HCs. The AN group showed significantly higher mean and maximum levels of aversive tension. Crucially, in the AN group, reported food intake was associated with higher levels of aversive tension, whereas school or sport-related events were not specifically linked to aversive tension in this group. This study highlights how EMA can pinpoint specific contextual triggers for negative affective states in AN. Using smartphone-based EMA in an epidemiological cohort, findings suggested that experiential avoidance was temporally linked to greater engagement in disordered eating behaviours (DEBs), supporting theories that DEBs may serve an avoidance function for unpleasant inner experiences (Peschel et al. 2023). This type of research demonstrates EMA's capacity to examine the micro-processes and maintaining mechanisms of ED symptoms relevant to AN. The general utility of EMA lies in its ability to capture momentary snapshots of daily life, providing rich, contextualised data on the antecedents and consequences of ED behaviours and associated affective states (Shiffman et al. 2008; Goldschmidt et al. 2018; Drexl et al. 2025). These methods can inform 'just-in-time adaptive interventions' (JITAIs) (Smith et al. 2019; Linardon and Torous 2025; Pavlacic et al. 2025).

3.15. Markers of physical health risk and refeeding markers

AN is a chronic disease with numerous psychiatric and medical comorbidities. It can affect all organ systems and thus leads to more serious physical harm than any other mental illness. The 2011 meta-analysis by Arcelus et al. (2011) provided an overview of the results of 36 studies. The mortality rate indicates the relative risk of a patient group compared to a similar population group. The studies reported outcomes of AN during 166 642 person-years, and the weighted mortality rates (i.e. deaths per 1000 person-years) was 5.1 for AN. The standardised mortality ratio for AN was 5.86. One in 5 individuals with AN who died had committed suicide (Arcelus et al. 2011).

This section explains the biological markers of the physical health risk associated with AN. Table 4 summarises these markers, the specific risk that they indicate and the direction of change.

3.15.1. Body measures as risk markers

Low weight has been a core feature of the definition of AN since its first modern-age description in the late nineteenth century (Gull 1997). A meta-analysis by Hübel, Yilmaz, et al. (2019) showed marked differences in weight and BMI between persons with AN and HCs. Low weight remains an essential diagnostic criterion for AN (APA 2013; World Health Organization 2024). In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), while the diagnosis of

Table 4. Overview of biological risk markers.

Parameter	Direction of change	Risk factor for	Comments	Citation
Body weight and composition				
BMI	↓	General morbidity, mortality	Risk increases continuously with lower BMI	(Cuntz et al. 2023; Gibson et al. 2024)
Recent weight loss	↑	Low prealbumin and reduced hand grip strength; bradycardia, lower pulse rate nadir		(Whitelaw et al. 2018; Gibson et al. 2024)
Weight suppression (discrepancy between highest adult weight and current weight)	↑	Increased likelihood of amenorrhoea, reduced systolic blood pressure, (nadir) haemoglobin; lower pulse rate nadir, bradycardia		(Whitelaw et al. 2018; Gibson et al. 2024)
BMI after treatment	↓	Relapse	A higher BMI/weight/body fat was associated with lower odds of relapse when it was assessed at discharge than when assessed at admission.	(Sala et al. 2023)
Rapidity of weight loss Weight loss rate	↑	Electrolyte abnormalities, dehydration, cardiovascular complications (such as bradycardia) and endocrine disturbances	Likelihood of an admission increases with increasing rate of weight loss and lower energy intake, independent of underweight.	(Brennan et al. 2024)
Fat mass	↓	Amenorrhoea (specifically associated with lower extremity fat mass)	Posttreatment fat mass and gain in fat mass during treatment are negatively associated with presence of amenorrhoea.	(Hübel, Yilmaz, et al. 2019)
% body fat	↓	Amenorrhoea	Fat percentage is a positive predictor of resumption of menses (but not superior measure to BMI).	(Winkler et al. 2017)
Metabolism				
Gonadal axis	↓	Amenorrhoea, osteopenia	caused by decreased energy availability in patients with AN	(Jada et al. 2021)
Adrenocorticotropic hormone (ACTH), cortisol, aldosterone	↑	Impaired glucose tolerance, elevated blood lipid levels., increased release of mineralocorticoids (=> hypokalaemia, increased water retention)	Indicators of activated HPA axis. HPA axis is activated to provide energy for the organism when energy intake is too low.	(Misra and Klibanski 2014; Schorr and Miller 2017; Thavaraputta et al. 2023)
Cholesterol	↑	The increased cholesterol is not the main reason for an increased cardiovascular risk in AN	Consequence of the activated HPA axis and the low T3 levels.	(Ohwada et al. 2006; Affaticati et al. 2023)
Thyroid hormones (T3, T4)	↓	Hypothermia, bradycardia, constipation		(Wu et al. 2024)
Body temperature	↓	Unclear, whether independent risk		(Brennan et al. 2023; Ralph-Nearman et al. 2024)
Resting metabolic rate	↓	Unclear, whether independent risk	Resting energy expenditure increases with increased energy intake and body weight.	(de Zwaan et al. 2002; Reed et al. 2024)
Blood glucose	↓	Hypoglycaemia, coma		(Gibson et al. 2020)
Glucose tolerance	↓	Impaired glucose tolerance predicts poorer refeeding outcome, (slower weight gain)		(Casper 1996; Yasuhara et al. 2005)
Cardiovascular system				
Heart rate	↓	Bradycardia is a risk factor for orthostatic collapse and syncope	Unclear whether dangerous	(Assalone et al. 2022; Jomah et al. 2024)
Tachycardia	↑	Heart failure	Seems to indicate high risk	(Krantz and Mehler 2004)
Blood pressure	↓	Orthostatic collapse		(Sekaninova et al. 2020; Jenkins et al. 2022)
QRS amplitude	↓	Indicates low left ventricular mass		
QT Interval*	↑	Potential risk indicator for ventricular arrhythmia	Explained by hypokalaemia or psychotropic medication	(Krantz et al. 2020)

(*Continued*)

Table 4. Continued.

Parameter	Direction of change	Risk factor for	Comments	Citation
Left ventricular mass	↓	might indicate risk of heart failure		(Kuwabara et al. 2018)
Pericardial effusion	↑	Pericardial tamponade	Mostly asymptomatic	(Kuwabara et al. 2018)
Water balance, electrolytes and hepatic markers				
Sodium	↓	Adynamia, coma, pontine myelinolysis	Mostly indicative for polydipsia	(Santonastaso et al. 1998; Lawson et al. 2012; Boyd and Durant 2018; Che Mokhtar et al. 2022)
Potassium	↓	Nephropathy, seizures, arrhythmias, TdP (Torsades de pointes)	More frequent in AN-BP	(Puckett 2023)
Phosphate	↓	Rhabdomyolysis Marker for refeeding syndrome – coma, death		(O'Connor and Nicholls 2013)
Creatin kinase	↑	Rhabdomyolysis Refeeding syndrome		(Stheneur et al. 2014; Riva et al. 2021; Tseng et al. 2023)
Creatinine clearance	↓	Renal failure		(Bouquegneau et al. 2012)
GFR	↓	Renal failure		(Bouquegneau et al. 2012)
Albumin	↓	Oedema		(Wu et al. 2024)
ALT/AST	↑	Coagulopathy, hepatic failure, death		(Kheloufi et al. 2014; Rosen et al. 2017; Cuntz and Voderholzer 2022)
Micronutrients/Vitamins				
Zinc	↓			(Winston 2012)
Iron	↓	Iron deficiency anaemia		(Winston 2012)
Folate	↓	Macrocytic anaemia,		(Patrick 2002; Castro et al. 2004; Winston 2012)
Vitamin B1	↓	Wernicke's encephalopathy		(Patrick 2002; Tam et al. 2022; Affaticati et al. 2023)
Vitamin B12	↑↓	Macrocytic anaemia, funicular myelosis	Several studies found increased vitamin B12 mean blood concentrations in people with AN, but vitamin B12 deficiency has also been reported.	(Hadigan et al. 2000; Tam et al. 2022; Affaticati et al. 2023)
Vitamin K	↓	Osteoporosis		(Urano et al. 2015)
Vitamin D	↓	Osteoporosis, fractures Bone density		(Mehler et al. 2018)
Hematologic parameters				
Erythrocytes	↓	Anaemia, weakness		(Hütter et al. 2009)
Haemoglobin	↓	Anaemia, weakness		(Walsh et al. 2020)
Haematocrit	↓	Water overload, oedema, anaemia		(Walsh et al. 2020)
Leucocytes	↓	Bacterial infections	Gelatinous bone marrow transformation	(Bowers and Eckert 1978; Schafernak 2016; Walsh et al. 2020; Keeler et al. 2025)
Thrombocytes (platelets)	↓	Coagulopathy		(Walsh et al. 2020)
NLR	↓	No specific risk known		(Bou Khalil et al. 2022; Caldiroli et al. 2023)
Ferritin	↑	No specific risk known		(Wanby et al. 2016)
Neurological (selected)				
EEG		No specific risk known		
Nerve conduction velocity	↓	No specific risk known		
Bone markers				
BMD	↓	High risk of bone fracture	Fat mass is associated with total BMD. Duration of amenorrhoea, age and illness duration are not significant predictors of BMD.	(Lucas et al. 1999)
IGF-I	↓	Independent predictor of BMD		(Barrios et al. 2024; Fazeli and Klibanski 2014)
Androgen	↓	Independent predictor of BMD		(Fazeli and Klibanski 2014; Thavaraputta et al. 2023)

Abbreviations: ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AN = anorexia nervosa; AN-BP = anorexia nervosa binge-purge subtype; AST = aspartate aminotransferase; BMD = bone mass density; BMI = body mass index; EEG = electroencephalogram; GFR = glomerular filtration rate; HPA = hypothalamic-pituitary-adrenal axis; IGF-1 = insulin-like growth factor 1; NLR = neutrophil-lymphocyte ratio; TdP = Torsades de pointes; ↑ = higher values or an increase indicate an increased risk, ↓ = lower values or a decrease indicate an increased risk, ↑↓ = increased or decreased are found in AN, and are both associated with a specific risk.

AAN is applied when all AN criteria are met except for the weight criterion, i.e. weight is within or above normal range. Regarding medical status, low weight is clearly associated with medical complications with markedly high risk in cases of BMI < 13 kg/m^2 (Cuntz et al. 2023). A recent retrospective study of an adult AN population (n = 761), found that while recent weight loss and weight suppression were associated with markers of malnutrition including low prealbumin, reduced hand grip strength, amenorrhoea and reduced systolic blood pressure, low BMI on admission was predictive of all markers (Gibson et al. 2024). Additionally, a recent meta-analysis found that low discharge weight was a good predictor of symptom recurrence and relapse. Stopping treatment too early has a poor prognosis. Admission weight did not play a significant role (Sala et al. 2023). For a synopsis of meta-analytic results for physical health risk and refeeding markers of AN see Tables S13 and S14, and for a synopsis of included studies on anthropometric biomarkers for AN see Table S15.

Nevertheless, accumulating data points to the dangers which may be overlooked in normal-weight restrictive disorders. A systematic review and meta-analysis of 8 studies including 2,331 participants with AN or AAN, found between 29 and 42% of participants presented with medical instability requiring hospitalisation in the absence of low BMI (Brennan et al. 2023). Another study following 205 AN/AAN patients in London clinics identified weight loss rate and low mean energy intake in patients requiring admission independent of underweight (Brennan et al. 2024). This is in line with previous studies of adolescents admitted for EDs, where about half of cases exhibited the atypical weight presentation (Fisher et al. 2015; Garber et al. 2019), and to weight loss again being associated with heart rate, a malnutrition marker (Whitelaw et al. 2018; Garber et al. 2019). Considering these data, it has been suggested that the straightforward weight criterion be omitted, and an evaluation of weight loss be considered (Phillipou and Beilharz 2019). In addition, the recently updated clinical description of AN in the International Classification of Diseases, 11th Revision (ICD-11) refers to patients' weight history and adds that rapid weight loss, such as loss of more than 20% of total body weight in 6 months, may replace the underweight criterion, provided all other criteria are met (World Health Organization 2024).

A recent retrospective study in 545 patients with severe AN or avoidant restrictive food intake disorder hospitalised in a medical stabilisation unit between 2018 and 2021 found a mean BMI of 13 kg/m^2 or less in 46% of patients with AN-R and in 39% with AN-BP. Hypoglycaemia was common and correlated with elevated liver function tests and low prealbumin. Refeeding hypophosphataemia developed in 26% of patients starting day 2 and was associated with lower BMI. Hypokalaemia appeared on admission among 39%, twice as common in patients diagnosed with AN-BP (Leach et al. 2024)

AN is a complex mental health and metabolic disorder. According to EWAS studies, for example, its biological features refer to cholesterol metabolism, lipid synthesis, the structure and stability of connective tissues, membrane transport and cell motility and the differentiation of brown adipose tissue and lipid metabolism (Booij et al. 2015; Kesselmeier et al. 2018; Steiger et al. 2019; Iranzo-Tatay et al. 2022; Steiger et al. 2023). In clinical settings, however, the attention is often focussed on underweight and malnutrition and their ramifications. With the obesity epidemic in the background in recent years data have been accumulating regarding AAN, which emerges as a comparable entity to AN, clinically and medically. This has led to suggestions that additional markers, including degree of weight loss and rate of weight loss, may be superior to BMI alone.

Of note, BMI alone, as a measure of weight in relation to height, is not sufficient to assess the individual risk of patients. In fact, the variance in morbidity and mortality is too large and it is necessary to identify other criteria that help to assess individual risk. AN can affect all organ systems, and individual risk markers should quantify the degree of organ involvement that contributes to individual risk.

3.15.2. Body composition, fat content

The meta-analysis by Hübel, Yilmaz, et al. (2019) provides a comprehensive evaluation of body composition changes in individuals with AN, highlighting significant reductions in fat mass and fat-free mass compared to HCs. Patients with AN had 50% lower fat mass, with a MD of −8.8 kg (95% confidence intervals [CI]: −9.81 to −7.79), and 4.98 kg lower fat-free mass (95% CI: −5.85 to −4.12) compared to HCs. During early weight restoration, fat mass was preferentially stored in the trunk region, differing from patterns in HCs. Furthermore, fat mass remained altered in AN, significantly lower than HC, even after weight restoration. Altered fat mass distribution has been described in AN with higher marrow adipose tissue and lower subcutaneous (SAT) and visceral (VAT) adipose tissue compared to HC (Fazeli et al. 2019). See sections 3.15.9 and 3.15.10 on bone marrow and bone markers.

Comparing constitutional thinness with AN, Bailly et al. (2021a) found that normal range fat percentages (around 18.9%) were retained in the former, whereas AN patients had significantly lower body fat percentages (~11.4%). However, fat free mass was similar between the two groups.

AN-associated alterations in body composition and fat distribution are linked to clinical outcomes like menstrual recovery, where a BMI of 19 kg/m^2 or a fat percentage of 23% predicts a 50% likelihood of resuming menses (Winkler et al. 2017). In contrast, constitutionally thin individuals do not show such disruptions, suggesting that hormonal and metabolic factors unique to AN play a pivotal role in these outcomes. Additionally, constitutionally thin individuals have not been reported to show alterations in thyroid parameters or bone density parameters.

3.15.3. Metabolic changes

Metabolism in AN is characterised by inadequate energy intake and the consequent need to conserve energy and to mobilise remaining energy reserves and make them available to the vital organs. This metabolic adaptation can be measured and verified on the one hand by a reduction in thyroid activity and the associated low T3 constellation and an increase in reverse T3 levels (metabolically inactive form of T3) as part of the euthyroid sick syndrome (ESS). ESS is a condition where thyroid hormone levels are abnormal in individuals with nonthyroidal illnesses, but the thyroid gland itself is functioning normally. This hormonal constellation leads to reduced energy consumption (bradycardia) and reduced production of body heat (hypothermia) (Misra and Klibanski 2014; Wu et al. 2024).

Mobilisation of energy reserves is triggered by activation of the HPA axis, as measured by increased basal cortisol levels. Consequences include impaired glucose tolerance and elevated blood lipid levels. In addition, increased HPA axis activity leads to release of mineralocorticoids and thus a tendency for hypokalaemia and increased water retention (Tey et al. 2005; Yücel et al. 2005; Ehrlich et al. 2006).

Thus, low T3, high basal cortisol levels, bradycardia, hypothermia, hypercholesterolaemia, a tendency to oedema and elevated postprandial glucose levels are all adaptive to ensure functioning of the organism in conditions of energy deprivation. On the one hand, they merely reflect the poor nutritional status and are not independent risk markers. On the other hand, these metabolic adaptations lead to dangerous changes in cardiac rhythm, electrolyte and water balance and glucose metabolism, which most likely contribute to the increased mortality in this group of individuals.

AN is associated with pathological glucose metabolism, including impaired glucose tolerance, stemming from HPA axis abnormalities and hypercortisolism (de Rosa et al. 1983; Casper 1996; Himmerich et al. 2010; Thavarapatta et al. 2023). For example, a case-control study by de Rosa et al. (1983) in patients with AN showed reduced basal glucose levels with a flat glucose curve and reduced insulin levels with a slight increase after glucose administration. A similar case-control study conducted by Fukushima et al. (1993) showed that patients with AN had lower fasting plasma glucose and insulin concentrations characterised by reduced insulin secretion, increased insulin sensitivity, and reduced glucose effectiveness (Fukushima et al. 1993). An observational study of interstitial glycaemic cycles showed that patients with AN had chronic, prolonged, mild hypoglycaemia over 24 h, including day and night, despite normal fasting glycaemia. This might be linked to the adaptive increase in counter-regulatory hormones to protect patients with AN from deeper hypoglycaemia (Germain et al. 2023). Furthermore, serum glucose levels increased significantly from admission to discharge (Puckett et al. 2024). During refeeding, the rapid shift from a starvation-adapted, catabolic state to a carbohydrate-rich, anabolic state can lead to paradoxically elevated insulin levels. This initial surge in insulin, is a key driver of refeeding syndrome and its characteristic electrolyte imbalances (Ponzo et al. 2021).

Refeeding syndrome is a critical metabolic complication characterised by severe electrolyte and fluid shifts following the reintroduction of nutrition in chronically malnourished patients, such as people with AN. Upon carbohydrate reintroduction, the subsequent glycaemic load triggers a rapid surge in endogenous insulin secretion. This anabolic stimulus drives the intracellular uptake of glucose alongside the electrolytes phosphate, magnesium, and potassium which can result in acute, life-threatening hypophosphataemia and associated systemic consequences, including cardiac arrhythmias and multi-organ failure (Gallagher et al. 2022).

Importantly, a single blood glucose measurement may miss ongoing hypoglycaemia. Thus, it has been suggested that haemoglobin A1C (HbA1c) (in addition to serum glucose) be measured as it reflects average blood glucose levels over the preceding 2 to 3 months (Puckett et al. 2024). Hypoglycaemia has been suggested to be a major factor in bradycardia, sinus arrest

and sudden death of patients with AN (Mehler et al. 2022). Since hypoglycaemia can be life-threatening, one of the tasks of treatment is to keep energy intake high enough to prevent hypoglycaemia.

3.15.4. Cardiovascular system

The severe energy deprivation associated with AN produces massive change in the cardiovascular system. Blood flow is centralised, arterial blood supply is reduced, and heart rate and blood pressure are decreased. The consequences of these changes can be inferred from the functional and morphological changes in the circulatory system, whereby, in terms of physical risk, a distinction must be made between changes that are merely adaptive, reducing energy expenditure, and thus only indicating the degree of underweight or weight loss, and those that indicate harmful consequences and thus are risk markers in the true sense. In severe cases, physical restraint, placement of a temporary pacemaker, or use of ionotropic or chronotropic medication might be indicated.

3.15.4.1. Functional cardiovascular changes. The resting electrocardiogram (ECG) in AN shows some abnormalities due to centralisation of circulation and smaller left ventricular muscle mass. As the pulmonary circulation remains unchanged in contrast to the systemic circulation, the ECG shows signs of relative right heart strain, i.e. a steep or right-sided type, more frequent incomplete right bundle branch block and a shift of the R/S transition to the left. Peripheral low voltage and a decrease in QRS amplitude indicate reduced left ventricular muscle mass. All these changes are adaptive and do not represent an independent risk.

Recurrent vomiting and misuse of diuretics and laxatives may lead to hypokalaemia, which can cause a significant risk of arrhythmias. Co-occurring hypercortisolism and hyperaldosteronism further intensify this tendency.

The risk of arrhythmia can be read from the ECG using the typical signs of hypokalaemia: T-wave flattening, preterminal T-wave negativisation, U-waves and QTc prolongation. These ECG changes make it possible to estimate the potassium voltage between extracellular and intracellular spaces. The higher the concentration gradient between cell and intracellular space, the higher the risk of cardiac arrhythmias, which can range from simple premature beats to ventricular fibrillation. These ECG changes therefore indicate a high cardiac risk.

Prolongation of the QT interval can lead to increased susceptibility to ventricular arrhythmias, including Torsade de Pointe (TdP) arrhythmias. For a long time, the high mortality rate in patients with AN was thought to be caused by fatal ventricular arrhythmias, which in turn were caused by the increased QT-dispersion associated with underweight (Cooke et al. 1994; Swenne and Larsson 1999). However, the relationship between underweight or weight loss and the QT interval is increasingly being questioned: in a 2008 meta-analysis, although a prolonged QT interval was found in AN compared with HCs, the QTc remained within the normal range and showed no pathological prolongation (Lesinskiene et al. 2008). It is possible that the finding of a relative prolongation of the QT interval is due to the correction formulae used, which do not sufficiently consider the high tendency to bradycardia in AN (Walter et al. 2015).

It is still considered likely that the increased mortality in AN is also caused by the occurrence of fatal ventricular arrhythmias (Mehler et al. 2022). It has been suggested that the QT interval may be responsible for some of these events. It has also been observed that in individuals with AN, the QTc interval fails to shorten with exercise and increased heart rate, contrasting significantly with the typical physiological response seen in HCs (Janzen et al. 2020). Prolongation of the QT interval is more common with medication (Gibson et al. 2020), and electrolyte imbalances (Bomba et al. 2018), may also contribute (Geer et al. 2019). Another theory is that low basal metabolic rate and increased vagal tone contribute to increased QT variability, which ultimately increases the risk of ventricular arrhythmias (Koschke et al. 2010).

Ultimately, the QT interval is obviously not only prolonged by malnutrition. However, since other factors accompanying AN can prolong the QTc time and this prolongation is associated with an arrhythmia risk, the QTc should be determined in patients with AN.

As an adaptation to low body weight and low Triiodothyronine levels, adolescent girls with AN showed significantly lower heart rates, lower systolic blood pressure, and lower body temperature compared with control subjects (Misra et al. 2004). Underweight adolescents with AN are significantly more likely to have lower blood pressure and bradycardia (Brennan et al. 2023). A systematic review showed lower heart rate (HR) and higher heart rate variability (HRV) in AN compared to HCs (Ralph-Nearman et al. 2024).

On the ECG, bradycardia usually appears as sinus bradycardia (Brennan et al. 2023; Jomah et al. 2024). However, supraventricular replacement rhythms, sinoatrial blocks and atrioventricular block patterns are

also rarely seen (Kanbur et al. 2009; Cussen and Harding 2021). In most cases, these bradycardic rhythm disturbances do not result in syncope; usually there is only mild orthostatic dysregulation. With exercise, the heart rate increases, and the block patterns are reversible. A pacemaker is therefore rarely required (Sall and Timperley 2015). Nevertheless, bradycardic arrhythmias are thought to possibly contribute to the mortality of patients.

3.15.4.2. Structural heart changes. Malnutrition, low weight, metabolic changes and centralisation of the circulation also lead to morphological changes in the heart that can be detected by echocardiography in patients with severe forms of AN (Smythe et al. 2021).

Essentially, these changes consist of

1. The muscle mass of the heart, particularly of the left ventricle, is reduced.
2. This is associated with changes in the diastolic and systolic function of the heart.
3. Mitral and tricuspid regurgitation are more common.
4. In more severe underweight, pericardial effusions are regularly observed.

The lower the weight, the lower the muscle thickness of the left ventricle. The left ventricular mass is significantly reduced, and septum and posterior wall are significantly thinner. Biopsy of the myocardium shows increased connective tissue transformation in severe AN (Lamzabi et al. 2015; Kuwabara et al. 2018; Smythe et al. 2021).

It has been shown that the ejection fraction of the left ventricle usually remains normal. Recent studies using global longitudinal strain to measure left ventricular systolic function have yielded conflicting results. The presence of global systolic dysfunction in AN and reduced left ventricular muscle cannot be confirmed by this method (Justine et al. 2022; Gherbesi et al. 2024). On the other hand, diastolic dysfunction can be regularly detected (Jomah et al. 2024).

There is an increased incidence of discrete mitral and tricuspid valve regurgitation in AN. Cases in which these insufficiencies require intervention are extremely rare (Borgia et al. 2021; Santangelo et al. 2022).

The lower the weight, the more common pericardial effusions are in patients with AN. These disappear with weight gain and are usually without haemodynamic significance (Docx et al. 2010).

These echocardiographic findings suggest that the ability of the myocardium to compensate for increased stress is reduced. There are few mechanisms available to adapt to the stress caused by a decrease in intravascular volume. Circulation is already largely centralised. Myocardial contractility is very limited. The only way to maintain adequate circulation is to increase heart rate. Tachycardia is therefore a risk marker for impending heart failure (Krantz and Mehler 2004).

3.15.5. Micronutrient deficiency

AN is associated with deficiencies in micronutrients, such as zinc, copper, vitamin C, riboflavin, and vitamin B6 (Winston 2012). A retrospective study of the medical records from 1,026 adult patients with EDs who were newly admitted to inpatient or residential care, found that 30.0% of patients had vitamin D deficiency (Mehler et al. 2018). In an observational study of 29 patients, 14 had developed vitamin A deficiency and 12 hypercarotenaemia (Silverman 1974). Plasma vitamin B12 levels are often elevated in more severe forms of AN. It has been suggested that there is a need for future investigation of vitamin B12 as a potential biomarker of severity, probably due to liver involvement (Tam et al. 2022; Affaticati et al. 2023).

Another study found zinc, copper, and iron binding protein deficiencies, and suggested hypogeusia may result from self-imposed nutritional restriction and lack of zinc (Casper et al. 1980). Yet another study found that adolescent patients with AN presented with nutritional abnormalities such as folate and zinc deficiencies, but none had severe vitamin deficiencies (Castro et al. 2004). Most deficiencies persisted after short-term weight recovery. Furthermore, folic acid deficiency may account for the persistence of anaemia (Castro et al. 2004). A cohort study in patients with untreated AN showed vitamin D deficiency was present in over one-third of patients and a strong relationship between vitamin D status and hip bone mineral density (BMD) values with benefits for those with 25OHD levels above 20 ng/ml (Gatti et al. 2015). The majority of patients with EDs had at least one micronutrient deficiency. The most common micronutrient deficiency was zinc (64.3%), followed by copper (37%) and selenium (21%) (Hanachi et al. 2019). The two most frequent vitamin deficiencies were vitamin D and vitamin B1 for 54.2% and 15% of patients, respectively. When comparing the two subtypes of AN, selenium and vitamin B12 levels were lower in AN-BP patients, while copper level was lower in AN-R (Hanachi et al. 2019).

One review suggested that, despite controversy, elevated serum vitamin A levels were attributed to inadequate intake of other nutrients required for vitamin A metabolism (should this be catabolism). Furthermore, food restriction in AN can lead to low

plasma thiamine levels. Vitamin B9, folic acid and Vitamin B12 deficiency have also been reported in patients with ED (Patrick 2002; Díaz-Marsá et al. 2017).

Although it is still unclear whether the above described vitamin and trace element deficiencies have any clinical significance, experts agree that the prophylactic administration of thiamine is useful, at least during the refeeding phase (da Silva et al. 2020; Preiser et al. 2021). Thiamine plays an important key role in carbohydrate metabolism and is needed to produce energy *via* the Krebs cycle.

3.15.6. Water and electrolyte balance

Considerable shifts in water and electrolyte balance occur in the context of EDs, especially AN and BN. Abnormal eating habits often also involve drinking behaviour, with polydipsia (to suppress hunger or increase weight) and water restriction (to decrease weight). Recurrent vomiting leads to volume loss, loss of chloride and other electrolytes and metabolic alkalosis. Abuse of diuretics and laxatives also leads to volume deprivation and shifts in electrolyte balance, particularly hypokalaemia and sodium loss, but not hypochloraemia. While disturbed regulation of electrolyte balance in EDs also affects other electrolytes such as magnesium, chloride and calcium, potassium, sodium and phosphate are particularly important for assessing risk. Additionally, in general, it is important to recognise that electrolyte aberrations are much more common in those with purging behaviours versus those with restrictive eating.

Physical exercise can additionally exacerbate water and electrolyte disturbances in people with AN by water and electrolyte loss through sweat, dehydration, hyponatraemia and hypokalaemia, and rhabdomyolysis (El Ghoch et al. 2016; Quesnel et al. 2023).

3.15.6.1. Potassium. Hypokalaemia in the context of EDs is most frequently caused by recurrent vomiting, which leads to hypokalaemia *via* renal compensation of the associated alkalosis (Mehler and Walsh 2016). Diuretics and laxatives can also lead to a direct loss of potassium. In cases of severe purging behaviour, the associated hyperaldosteronism plays a major role (Lai et al. 2017).

The loss of potassium initially affects the extracellular potassium concentration, while the intracellular potassium concentration is less affected. This causes an increase in the potassium voltage of muscle and nerve cells and thus an increased electrophysiological excitability of these cells. The rate of potassium loss is decisive for the level of the resulting potassium voltage. Chronic potassium loss also leads to a drop in intracellular potassium concentration and thus to a less pronounced change in potassium voltage. The risk of cardiac arrhythmia is therefore less pronounced with chronic potassium loss than with acute potassium loss. The ECG changes associated with hypokalaemia (Khan et al. 2007) allow estimation the resulting potassium voltage and thus the arrhythmogenic risk.

Hypokalaemia in the context of AN (Sugimoto et al. 2003) or in the context of diuretic abuse (Copeland 1989) is thought to account for case reports for the severe complication of pontine myelinolysis, even if there was no concomitant hyponatraemia. There are also case reports of rhabdomyolysis (Dive et al. 1991). Chronic hypokalaemia combined with volume and substrate deficiency are the conditions for the development of hypokalaemia nephropathy (Bouquegneau et al. 2012; Stheneur et al. 2014). This disease is characterised by tubulointerstitial fibrosis, which is clinically expressed as polyuria and metabolic alkalosis, and can result in end-stage renal disease and the need for haemodialysis.

In patients with AN-BP, recurrent or chronic hypokalaemia may eventually lead to hypokalaemic nephropathy and the development of end stage renal disease (ESRD). Because of the deleterious effect of prolonged hypokalaemia on the kidneys, patients with AN-BP and AN patients who regularly use over-the-counter laxatives have an elevated risk of poor renal outcomes (Khatri et al. 2023).

3.15.6.2. Sodium. A relative excess of water in relation to sodium manifests itself in laboratory values as hyponatraemia. It is caused by significantly increased water intake (primary polydipsia) and/or impaired water excretion, e.g. due to advanced renal insufficiency, excessive release of antidiuretic hormone (ADH), or inability to renally clear free water due to severe weight loss.

The more acute the hyponatraemia, the greater the risk of complications and the greater the need for aggressive therapy. Serum sodium levels above 130 millimoles per litre (mmol/l) (or 130 milliequivalents per litre [mEq/L]) are considered 'mild hyponatraemia', levels between 120 mmol/ and 130 mmol 'intermediate'; and levels below 120 mmol/l (or 120mEq/L) are considered severe. Clinical symptoms include nausea, malaise, headache, lethargy and possibly seizures. In extreme cases of hyponatraemia, coma and respiratory arrest (< 115 to 120 mEq/L) and non-cardiogenic pulmonary oedema may occur. Extreme hyponatraemia can lead to herniation of the brain stem, which is the most feared complication of hyponatraemia.

The urgency and aggressiveness of treatment depend on symptom severity, the acuity of the hyponatraemia, the level of serum sodium concentration and the patient's underlying disease. Care must be taken not to correct hyponatraemia too quickly, as this can lead to significant neurological damage (osmotic demyelination syndrome and pontine myelinolysis), especially in patients with chronic hyponatraemia.

3.15.6.3. Phosphate. One of the most feared complications of refeeding is refeeding syndrome. To understand what happens during refeeding, intracellular phosphate concentration is crucial (Cuntz et al. 2022; Medicine 2022). Much of the aetiology of refeeding hypophosphataemia is due to increased glucose supply causing insulin secretion which, in turn, drives phosphorus to move intracellularly (Medicine 2022).

However, intracellular phosphate deficiency might play an additional relevant role. The intracellular phosphate concentration is normally about 14 times higher than in serum. The concentration gradient is maintained by an active transport mechanism. The recovery of cellular metabolism during refeeding requires the availability of intracellular phosphate to produce energy-rich phosphates. In severe cachexia, the concentration gradient between serum and cells is significantly lower, i.e. serum levels provide an inadequate estimate of available phosphate.

Intracellular phosphate deficiency has detrimental effects on all organs and systems (Subramanian and Khardori 2000). In the heart, impaired contractility and reduced cardiac output lead to ventricular arrhythmias and heart failure (Kohn et al. 1998). Muscle dysfunction in various tissues may result in ophthalmoplegia, dysphagia or ileus; rhabdomyolysis may cause severe muscle pain and weakness or tubular necrosis along with impaired diaphragmatic contractility and respiratory paralysis. Neurological symptoms may include confusion, delirium, convulsions, tetany or coma (Dive et al. 1991; Wada et al. 1992; Walder and Baumann 2008). At the latest when symptoms occur or when creatine kinase rises, as an indication of rhabdomyolysis, phosphate should be substituted orally or, if necessary, parenterally. It is better to supplement oral phosphate prophylactically at the start of refeeding (Gallagher et al. 2022).

3.15.6.4. Water balance. When nutrition begins to normalise as part of treatment, many patients with AN show a pronounced tendency to oedema, characterised by a disproportionate increase in extracellular volume (Ehrlich et al. 2006; Rigaud et al. 2010; Fortune and Kaplan 2012). The weight gain due to oedema formation can be up to 10 kg and often unsettles patients and therapists alike and must therefore be included in the assessment of weight progression.

In principle, one can distinguish between oedema formation with refeeding and oedema due to Pseudo Bartter syndrome (PBS) which is defined as hypokalaemic hypochloraemic metabolic alkalosis in the absence of renal tubular pathology. PBS is a result of hyperaldosteronism secondary to volume depletion from purging behaviours (Thavaraputta et al. 2023). The activation of this mechanism leads to significantly increased water retention and a tendency to hypokalaemia under conditions of normalisation of the diet. In less pronounced cases, informing the patient of the benign nature of the oedema formation and a wait-and-see approach are sufficient, as the PBS normalises completely within the first few weeks. If oedema is pronounced, diuretic treatment, in this case with aldosterone antagonists, should be considered. However, diuretic treatment contributes to a delay in normalisation of renal function.

Pathophysiologically, other factors have been implicated in oedema formation. These include the reintroduction of insulin secretion combined with increased insulin sensitivity, leading to sodium retention in the distal tubule (Yücel et al. 2005). In cases with hyponatraemia, the syndrome of inappropriate ADH secretion (SIADH) due to pharmacological treatment should also be considered – SIADH is also thought to occur more frequently in AN (Challier and Cabrol 1995).

3.15.7. Renal function

The basic function of the kidneys is to remove harmful water-soluble substances from the body while maintaining electrolyte and water balance and regulating pH. The kidneys are very sensitive to malnutrition, partly because they are a highly active organ with a high oxygen demand and therefore a high energy requirement. Blood flow to the kidneys is very high compared to other organs, accounting for about 20-25% of cardiac output to support the task of filtering urine. Therefore, in addition to the direct damage to the kidneys from malnutrition, the volume depletion seen in ED (e.g. due to oligodipsia or repeated vomiting) also threatens renal function.

Renal dysfunction is common in ED patients who are admitted to hospital. Approximately 70% of patients show signs of acute renal failure, including the above-mentioned electrolyte disturbances and impaired osmoregulation. Clinically, this manifests as a decreased filtration fraction and impaired ability to

concentrate urine (Aperia et al. 1978). Renal function is usually assessed clinically by glomerular filtration rate (GFR), which is low in approximately one third of hospitalised patients with AN (Gurevich et al. 2021; Riva et al. 2021). However, GFR is calculated from creatinine, which is low relative to the loss of skeletal muscle mass in AN and is therefore likely to underestimate the degree of renal insufficiency.

Chronic renal failure is not uncommon in patients with AN (Puckett 2023; Tseng et al. 2023). A study conducted a 21-year follow-up of 84 patients after their first hospitalisation for AN and reported that 5.2% of the patients had chronic renal failure requiring haemodialysis (Zipfel et al. 2000). The most likely cause of chronic renal failure in AN is chronic hypokalaemia associated with volume and substrate depletion, which sets the stage for the development of hypokalaemia nephropathy. This disease is characterised by tubulointerstitial fibrosis, and clinically manifested by polyuria, metabolic alkalosis, proteinuria and consequent progressive renal failure (Bouquegneau et al. 2012). On the other hand, renal function is also affected by the occurrence of nephrolithiasis and, more rarely, nephrocalcinosis (Roberts et al. 2005; Denburg et al. 2017).

3.15.8. Liver function

Elevated transaminases are a common laboratory finding in patients with AN, with a correlation between the degree of malnutrition and transaminase levels (Rosen et al. 2017; Cuntz and Voderholzer 2022). Extremely underweight patients with AN are at risk of developing life-threatening liver failure (Furuta et al. 1999; Dowman et al. 2010; Chen et al. 2023). Such cases are additionally characterised by coagulopathy (International Normalised Ratio [INR] > 1.5) and/or hepatic encephalopathy, which are present alongside significantly elevated liver values. These symptoms are initially mild and manifest as behavioural changes, slight confusion, slurred speech and sleep disturbances. However, they can progress to coma. An improvement in the nutritional situation and provision of sufficient energy has been shown to lead to a rapid improvement of liver function. When the transaminases return to normal levels, INR and encephalopathy severity also improve.

The mechanism behind the observed abnormalities in liver function tests appears to be hepatic autophagy. The underlying cause of autophagy and the subsequent elevation of transaminases is the energy deficiency caused by AN, which forces liver cells to obtain energy through self-digestion. Histological examination typically shows the absence of portal fibrosis or periportal inflammatory infiltrates, while ultrasonography shows a normal echogenicity pattern without anomalies. Conversely, microscopic analysis reveals the presence of autophagosomes in vesicular intracellular compartments containing secreted material from cell organelles such as mitochondria or endoplasmic reticulum (Kheloufi et al. 2014).

Hypoglycaemia may be a sensitive indirect marker of impending hepatic damage as individuals with AN and starvation-induced hepatitis are at increased risk of hypoglycaemia due to depleted glycogen stores and impaired gluconeogenesis (Rosen et al. 2017).

3.15.9. Bone marrow suppression

The energy requirements of the bone marrow for production and ongoing turnover of cells in the circulating blood is high. It is therefore not surprising that the chronic energy deficiency associated with AN leads to a significant reduction in the regenerative activity of bone marrow cells, affecting all cell lines (Walsh et al. 2020). These findings are more pronounced the greater the degree of underweight. The bone marrow is converted into a thick mucopolysaccharide with serous fat atrophy, a process known as gelatinous bone marrow transformation (Schafernak 2016; Shergill et al. 2017).

Anaemia is frequently present, especially in severely underweight patients, and can be very pronounced (Cuntz et al. 2022). Consistent with the reduced cell proliferation rate of the bone marrow, the anaemia is usually aplastic. Iron deficiency is rarely a cause, although many of the patients eat a vegetarian diet and therefore consume less iron. As many patients are amenorrhoeic, the iron loss is lower. It should be noted that ferritin is paradoxically elevated in many cases and does not allow a reliable estimate of the iron supply (Wanby et al. 2016).

Among the frequent changes in blood values in patients with AN are reductions in cell counts, especially leukocytes (Keeler et al. 2025), which are often reduced depending on the severity of the underweight. Leukocytes, especially granulocytes, are necessary for defence against bacterial infections. Infection represents a significant health risk. Therefore, leukocytes should be regularly monitored. However, the actual risk of infection has not been systematically investigated, so only case reports can be referred to (Birmingham et al. 2003; Brown et al. 2005).

Typically, leukocytopenia is the most noted blood count abnormality, followed by anaemia and thrombocytopenia (Walsh et al. 2020).

3.15.10. Bone markers in an

In AN, a state of chronic energy deprivation leads to compromised bone health and alterations in bone markers which may persist after treatment and nutritional stabilisation (Puckett 2023). BMD, the main indicator of bone health is measured by dual-energy X-ray absorptiometry (DXA) and is described in Z scores compared to age and sex matched HCs, with osteopenia defined as a BMD between −1.5 and −2.5, while osteoporosis is defined as a BMD < −2.5.

Several meta-analyses have shown that individuals with AN have significantly lower BMD compared to HCs (Robinson et al. 2016; Solmi et al. 2016; Lopes et al. 2022). In a meta-analysis of eight studies (Solmi et al. 2016) reported that 21.6% of individuals with AN had osteoporosis, while 45% had osteopenia. For a synopsis of meta-analytic results see Table S16. More recent large cohort studies with at least 300 patients with AN have found low BMD rates of 40-70% (see Table S17; (Workman et al. 2020; Leach et al. 2024)). BMD has been found to be lower in AAN than HCs, and though results have been inconsistent, larger studies have found higher BMD in AAN compared to AN (Nagata et al. 2019; Tuli et al. 2023; Davis et al. 2024). Low BMI, long illness duration, longer periods of amenorrhoea, late menarche age and body composition were all found to predict low BMD in many, but not all studies (Solmi et al. 2016; Workman et al. 2020; Bemer et al. 2021; Lopes et al. 2022; Tuli et al. 2023). Follow-up studies have described low BMD in some AN patients five-20 years after onset of AN, but these studies are few and small in scale (Jagielska et al. 2017; Mumford et al. 2019). Risk of osteopenia and osteoporosis is also increased by comorbid depression (Ji et al. 2024) and potentially psychotropic medications like selective serotonin reuptake inhibitors (SSRI) (Zhou et al. 2018) and antipsychotics (Al Jumaili and Jain 2025).

The risk of fractures is another critical concern in AN. In a meta-analysis of six studies, (Solmi et al. 2016) found that AN patients had a significantly higher overall fracture risk compared to HCs, with an odds ratio (OR) of 1.84 ($p = 0.008$) across all skeletal sites. A large retrospective cohort study from Denmark found that risk of fractures was highest in patients with active AN compared with recovered patients, who had a higher risk than that of HCs, but no association between fracture risk and BMD (Frølich et al. 2020a, 2020b).

Vitamin D is essential for bone health, and its deficiency can exacerbate bone loss. A meta-analysis by found individuals with AN that did not receive supplementation had significantly lower levels of (Veronese et al. 2015) 25OH-D compared to HCs. In contrast, patients with AN who received Vitamin D supplementation had higher levels compared to HCs. Interestingly, there was no significant difference in dietary Vitamin D intake between AN patients and HCs.

Bone turnover markers in patients with AN are disturbed, showing different levels than HCs and altered relationships with other bone markers or related hormones or regulatory factors. Reductions in bone formation i.e. dickkopf-1 protein (DKK-1) or IGF-1 have been demonstrated, along with increased bone resorption (Maïmoun et al. 2020; Maïmoun et al. 2014). Weight restoration has been associated with increase in bone formation markers i.e. bone-specific alkaline phosphatase (BALP) and N-terminal propeptide of type 1 procollagen (P1NP) and decreased resorption markers such as C-terminal collagen cross-links (CTX)(Giollo et al. 2017).

Adipose Tissue and Bone Marrow Fat have been explored with altered fat distribution described, including higher marrow adipose tissue and lower SAT and VAT compared to HC (Fazeli et al. 2019).

In terms of clinical management, the primary approach involves nutritional rehabilitation and weight restoration. Additionally, there may be a role for use of long-term bisphosphonate use in adult women with AN, and hormone replacement therapy (HRT) but more research is required (Robinson et al. 2016).

3.16. Therapeutic drug monitoring and pharmacogenetics

Therapeutic drug monitoring (TDM) is an important measure for quality assurance in adolescent and adult patients receiving psychoactive drugs like antipsychotics, antidepressants or mood stabilisers (Egberts et al. 2015; Gerlach et al. 2016; Hiemke et al. 2018; Unterecker et al. 2019; Eap et al. 2021; Schoretsanitis et al. 2021; Wesner et al. 2023). TDM uses rigorous measures of therapy surveillance including reliable measures of adverse events and taking serum levels (and interpreting them) of the drugs in use in the individual patient in routine treatment for maximising safety and quality assurance (Egberts et al. 2020). In particular in minors, TDM is helpful and recommended as most treatments are off-label (Egberts et al. 2022) and there is only preliminary data on age-specific reference ranges for serum levels in minors in general and in EDs in particular (Fekete et al. 2020).

In patients with AN all phases of pharmacokinetics may be affected. Changes in gastrointestinal tract function, such as delayed gastric emptying and altered

intestinal motility, can lead to unpredictable absorption of oral medications. Laxative use (which is common among adolescents with AN) may intensify abnormalities of drug absorption (Turner et al. 2000). Loss of body fat and muscle mass alters the volume of distribution (Vd) of medications. With reduced fat stores, lipophilic drugs will have a smaller volume of distribution and increased concentrations in blood (van den Berg et al. 2023). Liver function, in particular the activity of cytochrome P450 enzymes (CYP), can be impaired in AN. In 24 patients with AN, the metabolic activity of CYP3A4 was decreased, whereas the metabolic activity of CYP1A2 was increased (Sandvik et al. 2020). Such changes will affect drug concentrations and may change the effectiveness and tolerability of drugs. Altered pharmacokinetics require individual dose adjustment when treating patients with AN, best done in conjunction with TDM (Hiemke et al. 2018).

However, to date, TDM has been rarely used in AN or other EDs. Regarding olanzapine, most studies have been small (Fekete et al. 2017), AN: $n = 37$, BN: $n = 2$; (Bachmann et al. 2008) AN: $n = 5$; (Theisen et al. 2006) AN: $n = 13$). A recent larger study proved the potential of TDM of olanzapine in adolescents with AN. In this study, Karwautz et al. (2024) found a high correlation (0.72) of dosage and serum blood level, relatively few adverse events (6.3%), clinical improvement in 75% (Clinical Global Impressions [CGI]), and BMI-improvements (1.5 kg/m^2), and was able to define a preliminary disorder- and age-specific therapeutic reference range for olanzapine in adolescent AN (11.9 – 39.9 ng/mL). In an additional publication (Krauss et al. Submitted), that used the TDM-sample ($n = 47$) on olanzapine reported by Karwautz et al. (2024), the olanzapine group was compared with a sample receiving no olanzapine ($n = 47$). Patients in the olanzapine group (mean 9 mg/day) achieved greater weekly weight gain (0.898 vs. 0.677 kg, $p = 0.004$) compared to the group without olanzapine. Both groups showed similar reductions in ED pathology. The only study in adults that measured serum levels of olanzapine was an RCT where 75 participants were randomly assigned to receive up to 10 mg/day olanzapine, and 77 participants to receive placebo (Attia et al. 2019). This RCT found mean plasma levels of 21.0 ng/mL (standard deviation [SD] = 12.8) at week 8 and of 22.0 ng/mL (SD = 18.2) at week 16.

To date, only a single study used TDM for fluoxetine in minors ($n = 138$) including AN patients (Frey et al. 2023): $n = 13$). However, diagnosis-specific data on ED subsamples were lacking.

When serum levels vary among patients receiving the same drug dosage, investigating the genetics of the hepatic CYP system can clarify this variance. Such analysis helps identify why certain patients fail to achieve therapeutic thresholds – often due to rapid or ultrarapid metabolism or non-adherence – while others experience increased toxicity due to poor metabolism.

Despite its potential, pharmacogenetic research remains virtually non-existent in EDs including AN. By investigating specific genes within the CYP system that govern the metabolism of medications, researchers and clinicians could better understand individual pharmacokinetic profiles. Consequently, these insights could guide clinical decision-making to determine the optimal dosage for patients with AN.

4. Discussion

4.1. Summary and general comments

The biological markers of AN include genetic and epigenetic markers; neuroimaging markers of the brain; molecular markers of brain plasticity and brain damage; hypothalamic, gastrointestinal and adipose tissue-related signalling molecules associated with the regulation of appetite and metabolism; stress hormones; sexual and social hormones; immunological markers; metabolic and gut microbiome markers; neurophysiological and digital markers. Additionally, AN is associated with various physical health risks for which specific risk markers are in clinical use, for example body and body composition markers; metabolic, cardiovascular and nutritional markers; markers of water and electrolyte balance, renal, hepatic, bone and bone marrow markers as well as neurological signs and symptoms. Therapeutic drug monitoring and pharmacogenetics testing may identify markers related to the treatment of AN. Methods for the determination of these markers include neuroimaging, genetics and epigenetics, molecular diagnostics using blood or serum, saliva, CSF, faeces or urine samples, clinical and neurophysiological testing as well as digital methods such as actigraphy.

Only few of these biological markers seem to be causally linked to AN, such as genetic markers that convey a degree of risk of the metabolic and psychiatric features of AN (Bulik, Carroll, et al. 2021) as well as immunological markers such as auto-antibodies against α-MSH, ghrelin and leptin (Terashi et al. 2011; Espinoza-García et al. 2022; Seitz et al. 2024). Most of the biological markers including neuroimaging,

hormones, metabolomic, microbiomic, neurophysiological or digital markers are consequences of malnutrition.

Overall, the markers associated with AN are not used in clinical practice yet, and they are mostly not specific to AN. Only the physical risk markers in Section 3.15 are already in clinical use. However, they are not specific for AN, and rather indicate a specific physical risk as explained in Section 3.15.

For most of the markers there is a considerable overlap between the values found in people with AN and HC. Thus, none of these single markers can distinguish between AN and healthy people or between AN and patients with other diseases that might also influence these markers. A pattern of several markers in combination might be able to provide this distinction; however, such patterns have not been established. It is a challenge to ascertain whether biological markers are state or trait markers as we see some improvement after weight recovery, but a scar seems to remain.

Even though the neuroimaging, neuroplasticity, appetite-regulating, stress-related, metabolic, microbiomic and digital biomarkers are potentially not related to the causal factors of AN, they capture many aspects of the psychosocial, metabolic and behavioural symptomatology of AN. The reduction of GM volume and connectivity together with the impairments in neuroplasticity and neurogenesis have been suggested to be related to the difficulties in memory, bigger picture thinking and cognitive flexibility in people with AN (Keeler et al. 2021). The disturbances in hormones related to stress (e.g. cortisol), social bonding (e.g. oxytocin) and sexuality (e.g. LH) are linked to the relational difficulties, the social isolation and the loneliness that people with AN are experiencing (Sánchez-Sánchez and Rolland 2023). The microbiomic and metabolomic changes reflect the restricted diet and its limited variety. Additionally, the low leptin levels which induce an urge to exercise (Hebebrand et al. 2003) and the increased level of physical activity (Favaro et al. 2000) that can be measured using digital devices link to the over-exercise that people with AN often display. Even though these biomarkers are not specific to AN, they might inform the development of future biological therapies. The fact that these changes are rather consequences then causal factors in the pathophysiology of AN does not necessarily mean that they cannot serve as treatment targets. For example, several case reports have demonstrated that metreleptin might help to break the vicious cycle of malnutrition and the urge to exercise (Hebebrand, Plieger, et al. 2024).

Research on biological markers for the diagnosis and the treatment of EDs seems to be lagging other areas of psychiatry as it appears to have a large variance of psychological risks and drivers. In AD, the CSF biomarkers β-amyloid-42 (Aβ-42), P-tau, and Amyloid β 42/40 ratio are routinely used, particularly in the context of early diagnosis and the assessment of the risk of cognitive decline in subjects with mild cognitive impairment. Therefore, it is worth emphasising that the Neurochemical Dementia Diagnostics in AD is an example of a very well defined COU discussed briefly in the Introduction (Hansson et al. 2019; Dulewicz et al. 2022). Similarly, TDM and pharmacogenetic testing are already in clinical use in the pharmacological treatment affective and psychotic disorders (Hiemke et al. 2018), but the body of evidence in EDs is scarce.

There is no singular and generally accepted way to classify biomarkers. They could be classified based on how they are measured (e.g. neuroimaging, laboratory, electrophysiological, digital), based on the biological system level (molecular, cellular or tissue biomarkers) or where they are used in the diagnostic or therapeutic process (e.g. diagnostic, monitoring, outcome biomarkers). They can also be classified as biomarkers of risk, diagnosis or trait, state, stage, response and prognosis (Berk 2015; Davis et al. 2015). However, the current classifications use overlapping categories.

4.2. Genetics and epigenetics

EDs are finally coming to the fore in the genetic analysis, with increasingly large samples for meta-analyses enabling improvement in the understanding of the underlying genetic (and biologic) aetiology of AN, and in due course other EDs also. At this stage, much evidence supports the reconceptualization of AN both as a disorder of the mind/brain and the body i.e. a metabo-psychiatric disorder (Bulik et al. 2019; Watson et al. 2019).

It is also critical to highlight that genetic studies to date have focused on women (both twin and molecular). How genetic risk may differentially impact men is not yet clear. In the current GWASs only approximately 3% of the cases are men (Watson et al. 2022). There is some evidence, for example, that AN polygenic risk correlates with percent body fat differentially between men and women (Hübel, Gaspar, et al. 2019), as well as anthropometric genetic correlations being stronger in women (Duncan et al. 2017; Watson et al. 2023). With women dominating samples at this time in ED research, there is a need to expand to large male case cohorts, and as much as possible to

other gender groups, to establish if risk variants vary or are the same, and/or how polygenic predictors behave in these populations. This criticism also applies to gender and ancestry, with analyses overwhelmingly based on European-ancestry samples. The danger of lack of diversity in genetics is assuming that the same genetic factors influence disease risk across populations and developing therapeutics based on non-diverse GWAS that will ultimately increase rather than decrease health disparities (Huckins 2022). The PGC-ED is actively collecting genetic samples from individuals across ancestries to address this imbalance, and extending to BN, BED, ARFID, and OSFED. This initiative will help to identify genes and pathways that are shared across conditions as well as those that are specific, further clarifying the aetiology of EDs.

Regarding epigenetics, accumulating literature on DNA methylation in AN points to the intriguing possibility that several aspects of phenomenology in AN may be epigenetically regulated. With some consistency, available EWAS studies have documented probe-specific differences as to DNA methylation levels observed in individuals with active AN when compared to people who have either recovered from AN or who have never been ill with it. Differentially methylated regions identified in the studies in question tend to implicate genes involved in brain function, metabolism and immune response. Together, these results support an understanding of AN as having multiple (psychiatric, metabolic and immune) determinants, as would be consistent with the recently proposed conceptualisation of AN as being a 'metabo-psychiatric disorder' (Duncan et al. 2017; Watson et al. 2019). In addition, findings from available EWAS studies have revealed that differential methylation findings at some DNA sites appear to be replicable. The preceding is striking, given the low probability with which chance repeated identifications of the same genes (among tens of thousands of genes interrogated using high throughput microarray technologies) would emerge across independent studies.

Studies emerging from the Steiger/Booij group point to an additional possibility that altered DNA methylation levels may be most pronounced in individuals with lowest BMIs and longest durations of illness, and reversible with weight restoration. Together, such observations suggest potentials of DNA methylation changes as markers of illness staging, entrenchment and recovery. Should such effects be corroborated in future longitudinal studies, findings have potential to isolate genes (and biological systems they represent) that are involved in the development of and, more importantly, remission from AN symptoms.

We add a comment on limitations of the epigenetic literature in AN. Samples are invariably small, which calls the stability of findings into question and heightens risk of spurious observations. Also, given tissue specificity of DNA methylation, findings obtained using peripheral tissues have uncertain relevance to brain function (Edgar et al. 2017). Finally, none of the available EWAS studies apply measures of gene expression, without which functional significance of altered methylation levels observed remains uncertain.

As a clinician, it is key not to assume EDs are entirely genetically based, nor environmentally driven, but a complex, nuanced, interplay between the two that changes over critical developmental periods, including entry to puberty, entry into young adulthood, and in women, across the perimenopausal period (Klump et al. 2007; Klump et al. 2012; Wade et al. 2013b; Fairweather-Schmidt and Wade 2015). Twin studies indicate that interactions between genetic and environmental factors are important, with peer weight-related teasing posing a critical trigger of increased genetic variance (Fairweather-Schmidt and Wade 2017). In time, environmental contributors will be integrated into predictive models that also include polygenic risk, to better elucidate interactions, and the additive genetic and environmental contributions to EDs.

Molecular gene-environment interaction studies are yet to be meaningfully explored in EDs and will necessarily initially focus on the context of PRS. Ultimately, the hope is that PRS will have clinical applicability, most likely in combination with other risk factors, not only predicting risk of developing a condition, but also for screening, clarifying diagnoses, optimising treatment allocation, predicting treatment response and adverse reactions (Murray et al. 2021; Wray et al. 2021). Given the nature of PRS and clear limits in their utility to predict eating or other psychiatric disorders, they should never be considered tests to be used for such procedures as embryonic screening as this represents a serious misuse of science. The inappropriate commercialisation of PRS is not only a misapplication of the science but can also convey false promise and assurance to consumers who are seeking certainty in a domain where complexity is the rule. Nonetheless great promise stands in the integration of PRS into models with other risk factors to better identify those at risk, and target interventions in the future, and crucially to better understand the underlying pathogenesis of these conditions.

Ultimately, the promise of GWAS may lie in: 1) informing EDs nosology based on genetic factors; 2) understanding ways in which the various EDs are situated biologically vis a vis other psychiatric and metabolic conditions; 3) clinical application of PRS to inform treatment optimisation and personalisation; 4) provide an empirical approach to understand how genetic factors can render some individuals more vulnerable to environmental risk factors, i.e. genetics offering the best strategy to understand environment.

4.3. Neuroimaging

In summary, structural neuroimaging has revealed substantial and widespread alterations in the brain associated with AN particularly in the acutely underweight state. The available data point to significant reductions in measures of GM and alterations in the WM connectome. While neuroimaging shows promise in elucidating the neurobiology underlying AN, several limitations remain. Reliable relationships between structural measures and ED psychopathology, other than those linked to weight status, remain elusive. Future research incorporating multivariate analysis methods may offer more comprehensive and reliable representations of brain-behaviour relationships (Marek et al. 2022). The influence of important clinical variables, such as illness duration and clinical subtype, also warrants further investigation. Despite these challenges, neuroimaging research has provided vital insights into how the brain is affected by acute AN and dynamically changes following weight restoration. As neuroimaging methods and analyses continue to evolve, these techniques hold promise for uncovering brain processes that can be targeted in treatments to promote more sustained recovery from AN. Future research, especially in longitudinal and larger samples, is essential for clarifying the dynamic nature of both GM and WM changes and their relationship to clinical outcomes.

The same applies to functional neuroimaging and connectivity. Large-scale longitudinal studies are needed to identify robust neural functional markers associated with the development and maintenance of AN. Such studies will also help clarify the roles of factors such as sex, age, and illness severity.

4.4. Markers of neuronal and synaptic plasticity

Understanding the role of neuronal biomarkers, including tau, NFP/NFL, and synaptic markers, in EDs holds immense promise for advancing diagnostic accuracy, prognostic assessment, and treatment development in these challenging conditions. By elucidating the neurobiological alterations associated with AN and BN, researchers can pave the way for targeted interventions that address underlying neuronal dysfunction and promote recovery.

The investigation of neuronal biomarkers in EDs represents a cutting-edge area of research that offers profound insights into the intricate interplay between neurobiology and psychopathology. By harnessing the power of advanced neuroimaging techniques, biomarker analyses, and translational studies, scientists are poised to revolutionise our understanding and management of AN and BN, ultimately improving outcomes for individuals grappling with these debilitating disorders.

4.5. Connections and mutual influences of hormonal and metabolic markers

Even though we structured this consensus statement into different categories of biological markers, this is a somewhat artificial approach that does not match the pathophysiological reality where the regulatory and effector molecules of various systems interact.

For example, the restricted eating and increased physical activity lead to nutritional deficiency and, consequently, to reduced adipose tissue. As a result of the reduced fatty tissue, leptin production is reduced leading to a decreased production of FSH and LH with the consequence of amenorrhoea due to reduced follicle growth and ovulation. This mechanism is reversible along with weight restoration (Ballauff et al. 1999). Additionally, restricted eating leads to low blood glucose which activates the glucocorticoid cortisol, because cortisol release is part of the body's counter-regulatory response to maintain blood glucose levels (Lee et al. 2023). Together with the lack of the gonadotropic hormones FSH and LH, the increased cortisol production leads to osteoporosis with a loss of bone mass and an increased risk of fracture (Fazeli and Klibanski 2018). Additionally, a reduced sexual desire and sexual dysfunction in AN may be accounted for by low concentrations of gonadotrophins, hypoestrogenism, and elevated cortisol levels (Fichter et al. 1982).

Thus, there is, for example, an interaction between sexual and metabolic hormonal signals which explains the pathophysiological chain reaction from nutritional deficiency to physical health consequences such as amenorrhoea and osteoporosis.

4.6. Digital biomarkers

4.6.1. Actigraphy and accelerometers as digital biomarkers in an

The application of actigraphy and accelerometers as digital biomarkers in AN holds promise across several

clinical domains as diagnostic, monitoring and prognostic biomarkers (see Table 5).

While not primary diagnostic tools, objective physical activity and sleep patterns could serve as adjunctive diagnostic indicators or phenotypic markers. For instance, a distinct pattern of light activity (Lehmann et al. 2018) or a specific sleep chronotype (Wilcox et al. 2024) could contribute to a more nuanced diagnostic specification, especially in challenging cases or for differential diagnosis from other conditions that cause weight loss (Himmerich and Treasure 2024). These objective behavioural signatures could provide

Table 5. Candidates for digital biomarkers for anorexia nervosa.

Device	Index	Metric description	Findings in AN
Actigraphy (Accelerometers)	Physical Activity (Frequency, Intensity, Duration)	Objectively quantify human motion, providing date-time stamped information on how often, how intensely, and how long physical activity occurs. Metrics include step counts, energy expenditure, and time spent in sedentary, very light, light, moderate, and vigorous activity. Objective measures overcome the tendency for AN patients to overestimate PA in self-reports.	Excessive physical activity, often termed 'driven exercise', is reported in 30-80%. High levels of light activity early in treatment may indicate a higher risk for slower recovery or treatment resistance. Acute activity urges have been linked to lower early weight gain during inpatient treatment.
	Sleep Patterns	Actigraphy is particularly suitable for measuring various aspects of sleep, including sleep fragmentation, sleep efficiency, and napping sessions.	Specific sleep disturbances identified including insomnia, sleep fragmentation, low sleep efficiency, and an increased propensity for napping, an 'early riser' chronotype.
Smartphones	Total Screen Time	Objective tracking of the overall duration of smartphone use *via* built-in applications.	Higher smartphone screen time was found and positively correlated with overall ED psychopathology and body dissatisfaction General problematic smartphone use, rather than specific platforms like Instagram, might be more indicative of ED-related concerns.
	Diet and Fitness App Use	Engagement with applications designed for tracking diet (e.g. calorie counting) and fitness (e.g. weight tracking).	These apps can trigger or exacerbate ED symptoms and may reinforce unhealthy obsessions.
	Treatment Support App Patterns	Interaction data from apps designed for ED treatment support (e.g. Recovery Record), including frequency of meal logging, consistency of self-monitoring, types of emotions recorded, and engagement with coping skills modules.	App-augmented treatment associated with significantly larger weight gain for patients in low-weight categories Usage logs generated by these apps hold potential as dynamic indicators of treatment engagement, symptom fluctuation, or relapse risk.
	EMA: Affective and Behavioural Dynamics	Real-time self-reports of mood, thoughts, behaviours, and context delivered *via* the smartphone interface, capturing momentary snapshots of daily life.	Significantly higher mean and maximum levels of aversive tension. Reported food intake was associated with higher levels of aversive tension. Disordered eating behaviours may serve an avoidance function for unpleasant inner experiences.
	Passive Sensing: Mobility Patterns (*via* GPS)	Data collected from the phone's GPS sensor to track changes in daily movement range, time spent at home versus other locations, and patterns potentially indicative of social avoidance or excessive exercise routines. GPS is frequently used in general mental health digital phenotyping.	Changes in daily movement range, time spent at home versus other locations, avoidance of social situations (especially those involving food), or patterns indicative of excessive exercise routines.
	Passive Sensing: Social Interaction Proxies (*via* call/text logs, microphone)	Data from call/text logs and ambient sound captured by the microphone to infer changes in communication frequency or patterns that might reflect social withdrawal or isolation.	Changes in communication frequency or patterns that might reflect social withdrawal or isolation.
	Passive Sensing: Sleep Proxies (*via* light sensor, phone non-usage)	Inferences about sleep patterns drawn from data such as light sensor readings (reflecting light exposure patterns) and periods of smartphone non-usage, which can provide objective data on sleep patterns, potentially complementing actigraphy	Disturbances like insomnia or altered chronotypes.
	Passive Sensing: Device Usage Patterns (e.g. app switching frequency)	Beyond total screen time, patterns such as how frequently a user switches between different applications, which could offer subtle behavioural clues	Not detailed yet for AN in the provided sources.

Abbreviations: AN = anorexia nervosa; ED = eating disorder; EMA = ecological momentary assessment; GPS = global positioning system.

additional evidence to support a clinical diagnosis or characterise specific AN subtypes.

Continuous monitoring of PA levels (intensity, duration, frequency) and sleep parameters (efficiency, fragmentation) offers an objective means to track disease progression and response to treatment. Changes in these objective metrics could signal improvement or deterioration, allowing clinicians to make timely adjustments to therapeutic strategies. For example, a sustained reduction in problematic light PA or an improvement in sleep efficiency could objectively indicate a positive treatment response.

The observed negative association between light PA and psychopathological improvement (Alberti et al. 2013) suggests that specific objective PA patterns could serve as prognostic indicators for treatment outcome. Patients exhibiting certain activity profiles, particularly high levels of light activity early in treatment, might be at higher risk for slower recovery or treatment resistance. Similarly, the presence of acute activity urges has been linked to lower early weight gain during inpatient treatment (Halbeisen et al. 2024). These objective behavioural markers could help identify individuals who may require more intensive or tailored interventions.

Despite their promising potential, several challenges must be addressed for the widespread adoption and optimisation of these technologies. A significant hurdle is the methodological heterogeneity across studies, including variability in device models, placement, data processing algorithms, and outcome definitions (Alberti et al. 2013; Lehmann et al. 2018; de Rijk et al. 2024; Suau et al. 2024). This inconsistency limits the comparability and generalisability of findings, underscoring the need for greater standardisation in research protocols. Many existing studies, particularly pilot investigations, suffer from small sample sizes (Karr 2017; Lim et al. 2023), which limits statistical power and the generalisability of findings (de Rijk et al. 2024). Larger, well-powered studies are therefore imperative.

4.6.2. The potential of smartphone technology

Smartphones, with their widespread adoption and sophisticated capabilities, offer a unique platform for collecting diverse data streams relevant to an individual's behaviour and psychological state (Melbye et al. 2020; Almenara et al. 2022). Beyond dedicated accelerometry for physical activity (which was the focus of the above part), smartphones can provide data through:

- Usage Logs: Screen time, specific application usage patterns (Rozgonjuk et al. 2023).
- EMA: Real-time self-reports of mood, thoughts, behaviours, and context, delivered via the smartphone interface (Shiffman et al. 2008; Kolar et al. 2016; Peschel et al. 2023; Drexl et al. 2025).
- Passive Sensing: Data from inbuilt sensors such as global positioning system (GPS; location and mobility), microphone (ambient sound, social interaction proxies), light sensors (circadian rhythm proxies), and call/text logs (social connectivity) (Tregarthen et al. 2015; Harari et al. 2016; Insel 2017; Melbye et al. 2020; MacLeod et al. 2021; Onnela 2021; Almenara et al. 2022; Kilshaw et al. 2022; Aledavood et al. 2025; Linardon and Torous 2025).

This approach aligns with the broader concept of digital phenotyping, which aims to use data from personal digital devices to construct an individual's 'digital phenotype', offering insights into their real-world functioning and mental state (Tregarthen et al. 2015; Insel 2017; MacLeod et al. 2021; Onnela 2021; Almenara et al. 2022; Kilshaw et al. 2022; Rozgonjuk et al. 2023; Stierle et al. 2023; Linardon and Torous 2025).

4.6.2.1. Objectively tracked total screen time. A notable area of investigation involves the relationship between objectively tracked total smartphone screen time and ED psychopathology. A study by Rozgonjuk et al. (2023) examined 119 women, including 29 with a self-reported history of AN diagnosis. Using built-in smartphone applications like iOS Screen Time and Android Digital Wellbeing to track usage, the researchers found that objectively measured total smartphone screen time was positively correlated with overall ED psychopathology (measured by the Eating Disorder Examination Questionnaire, EDE-Q) and body dissatisfaction (measured by the Body Shape Questionnaire, BSQ) in the total sample (Rozgonjuk et al. 2023). Women with a history of an ED diagnosis also reported higher smartphone screen time compared to those with no such history (Rozgonjuk et al. 2023). Interestingly, while total smartphone use showed these correlations, objectively tracked Instagram use time did not show a statistically significant difference between those with and without an ED diagnosis history, and its link to ED symptoms was less consistent than that of total screen time (Rozgonjuk et al. 2023). This suggests that general problematic smartphone use, rather than engagement with a specific platform alone, might be more indicative of ED-related concerns (Rozgonjuk et al. 2023). However, it is important to note that specific subgroup analyses for the AN participants concerning their tracked overall smartphone screen time and its correlation with ED

symptomatology or body dissatisfaction were not detailed in the available documentation. The study also highlighted discrepancies between self-reported and objectively tracked technology use, emphasising the value of objective data (Rozgonjuk et al. 2023).

4.6.2.2. Impact of diet and fitness apps. The use of diet and fitness applications has also been identified as potentially problematic. Qualitative research suggests that these apps can trigger or exacerbate ED symptoms by heavily focusing on quantification (e.g. calorie counting, weight tracking), promoting overuse, and providing feedback that may reinforce unhealthy obsessions (Simpson and Mazzeo 2017). The constant availability and discreet nature of these apps on smartphones can facilitate continuous engagement with potentially harmful content (Simpson and Mazzeo 2017). One study found that college students who reported using diet and fitness apps had higher levels of ED symptoms, though this relied on self-reported app use rather than objective tracking (Simpson and Mazzeo 2017).

4.6.2.3. Usage patterns of treatment support apps. Smartphone applications designed to support ED treatment, such as Recovery Record, offer another avenue for data collection. These apps often allow users to self-monitor meals, emotions, thoughts, and behaviours (Fairburn and Rothwell 2015; Tregarthen et al. 2015). Research on Recovery Record has indicated that app-augmented treatment was associated with significantly larger weight gain for patients in low-weight categories (including AN) and a greater percentage of patients moving into a higher BMI class (Tregarthen et al. 2015). While these studies primarily evaluate the app as an intervention tool, the usage logs generated (e.g. frequency of meal logging, consistency of self-monitoring, types of emotions recorded before/after meals, engagement with coping skills modules) hold potential as dynamic indicators of treatment engagement, symptom fluctuation, or relapse risk. However, detailed analyses correlating specific patterns of app usage with clinical outcomes in AN are an area for future development. The concept of 'closed-loop interventions', where app data could trigger personalised support, is also relevant here (Smith et al. 2019; Linardon and Torous 2025).

4.6.2.4. Digital phenotyping and its potential for AN. Digital phenotyping aims to use these passively collected digital traces to draw inferences about an individual's psychological state and behavioural patterns (Tregarthen et al. 2015; Insel 2017; Smith et al. 2019; MacLeod et al. 2021; Onnela 2021; Almenara et al. 2022; Kilshaw et al. 2022; Rozgonjuk et al. 2023; Aledavood et al. 2025; Linardon and Torous 2025).

For AN, potentially relevant data types could include:

- Mobility Patterns (via GPS): Changes in daily movement range, time spent at home versus other locations, avoidance of social situations (especially those involving food), or patterns indicative of excessive exercise routines (Huckins et al. 2019; MacLeod et al. 2021; Onnela 2021; Kilshaw et al. 2022; Almenara et al. 2022; Cho et al. 2024; Linardon et al. 2025). GPS is one of the most frequently used sensors in general mental health digital phenotyping (Onnela 2021; Linardon et al. 2025)
- Social Interaction Proxies (via call/text logs, microphone for ambient sound): Changes in communication frequency or patterns that might reflect social withdrawal or isolation (Harari et al. 2016; Kilshaw et al. 2022; Aledavood et al. 2025)
- Sleep Proxies (via light sensor, phone non-usage patterns).
- Device Usage Patterns: Beyond total screen time, patterns like app switching frequency or keyboard dynamics (though research on keyboard dynamics for AN is not apparent in the provided material) could offer subtle behavioural clues (Bangamuarachchi 2023; Stierle et al. 2023)
- Artificial intelligence (AI) and ML are considered essential for analysing these complex data (D'mello and Kory 2015; Huckins et al. 2019; Smith et al. 2019; MacLeod et al. 2021; Almenara et al. 2022; Bangamuarachchi 2023; Aledavood et al. 2025; Linardon and Torous 2025; Woll et al. 2025)

High-quality original research studies using passively collected smartphone sensor data (excluding primary accelerometry) to derive AN-specific indicators are currently very limited (Juarascio et al. 2015; Linardon et al. 2025; Linardon and Torous 2025). Reviews often highlight the potential but note a lack of empirical studies in AN populations (Almenara et al. 2022; Linardon et al. 2025; Linardon and Torous 2025).

Objectively collected data such as actigraphy and smartphone-derived data might be useful candidates for digital biomarkers for AN. Future progress depends on multimodal data integration, advanced AI/ML application, longitudinal AN-specific studies, methodological standardisation, and robust ethical frameworks, all developed with patient-centred perspectives.

4.6.3. The combination of digital technologies for research in an

The evolving landscape of digital biomarkers and wearable technologies heralds a promising future for the diagnosis, monitoring, and treatment of AN. As we advance, the integration of these technologies with AI and ML algorithms will likely become more refined, offering unprecedented precision in understanding and predicting individual patient trajectories. Digital biomarkers are transforming the AN care landscape by allowing real-time personalised insights into the patient's behavioural and physiological patterns. Ranging from smartphone-based monitoring to virtual reality (VR) therapy and AI-driven interventions, such tools target AN core challenges such as social withdrawal, disgust and self-disgust emotional dysregulation and distorted body image. VR enables clinicians to provide complex exposure scenarios tailored for AN patients. These include engaging with avatars, practicing social eating, eliciting and measuring disgust and experiencing larger body sizes to manage weight-related distress (Keizer et al. 2016; Porras-Garcia et al. 2021; Bektas et al. 2023).

Smartphone-based digital phenotyping utilises passive data such as geolocation, screentime, and heart rate variability, and has shown promising value in detecting early warning signs factors links to the relapse of AN patients, specifically social withdrawal and psychological distress. When paired with EMA, such technology allows real-time tracking of behaviour fluctuations and mood, supporting clinicians in identifying when patients start to disengage from daily functioning or portray signs of cognitive rigidity around social settings and food. One example is Porras-Segovia et al. (2020), who highlighted how passive sensing and EMA could identify precursors to withdrawal and suicidal ideation, which are highly relevant given the risk of emotional dysregulation and suicidality in AN patients (Porras-Segovia et al. 2020).

In parallel, VR therapies have shown promise in treating AN-specific symptoms, specifically in addressing fear of weight gain, body image disturbances and cognitive distortions around self-perception. Behrens et al. (2023) discovered that repeated exposure to healthy-weight avatars in VR triggered strong emotional responses and reduced fear of weight gain in AN patients gradually. This suggests the ability of VR to desensitise patients to anxiety-provoking stimuli in a controlled immersive way (Behrens et al. 2023). Similarly, Brizzi et al. (2025) utilised VR body-swapping techniques to allow a hospitalised patient to experience embodiment in a health-weight body, which resulted in immediate reductions in negative self-beliefs and body dissatisfaction; common features in restrictive AN (Brizzi et al. 2025). Additionally, Ascione (2024) integrated attentional bias modification along with VR-based mirror exposure, leading to sustained improvements in anxiety, drive for thinness and body-checking behaviours at six-month follow up (Ascione 2024). These interventions represent a new frontier in exposure-based treatments and directly target cognitive-affective mechanisms specific to AN, such as anxiety-driven avoidance, perceptual body image distortion, and weight phobia.

Furthermore, AI-enabled digital health tools are advancing behaviour interventions by reducing avoidance, enhancing treatment engagement, and supporting day-to-day symptom regulation. For example, Recovery Record, is a mobile app facilitating real-time food and symptom logging, which supports in disrupting restrictive eating patterns by introducing real-time accountability and clinician feedback. In outpatient settings, it addressed comorbid affective symptoms and physical recovery by resulting in fewer emergency visits, decreases in depressive symptoms and higher rates of weight gain in AN patients (Palacios et al. 2024). Likewise, Therabot, a generative AI chatbot offered 24/7 conversational support for individuals at high risk of EDs and led to significant reductions in ED symptoms including shame, perfectionism, and rigidity. Hence, the ability to access therapeutic dialogue during moments of distress can reduce urges to restrict or engage in compensatory behaviours, reinforcing recovery motivation between therapy sessions and emotional safety (Heinz et al. 2024).

Nevertheless, the promise of such technologies must be tempered with caution. The failure of the National Eating Disorders Association's chatbot Tessa, which provided harmful advice by encouraging contradicting AN treatment protocols such as weight loss strategies and calorie restriction (500-1000 calorie deficit), highlights the ethical risks of integrating AI in sensitive clinical contexts without proper oversight. The suspension and backlash of the tool emphasise the critical need for continuous monitoring, clinical validation and ethical guardrails while developing AI-driven mental health support systems. As Torous and Nebeker (2017) argued, without such safeguards, digital tools can unintentionally reinforce disordered behaviours like compulsive exercise, food restriction, or body image distortion, thus worsening the conditions they aim to treat (Torous and Nebeker 2017). The iatrogenic risks of AI are being described in several psychiatric disorders (Østergaard 2025), but AN is foremost.

As future research continues to refine personalised, AI-driven interventions that adapt in real time to the needs of AN patients, the ethical, privacy, and data security aspects of digital health technologies will remain paramount. Robust frameworks are essential to safeguard patient information while enabling the innovations' transformative benefit. Furthermore, interdisciplinary collaboration between clinicians, technologists, patients, and policymakers will be crucial to ensure these solutions are accessible, equitable, and integrated into existing treatment ecosystems. Ultimately, the promise of digital biomarkers in transforming the care of individuals with AN lies in their ability to bridge gaps in current treatment paradigms facilitating early detection, personalised care, real-time support, and sustained recovery. By addressing the specific symptoms and treatment barriers of AN, such technologies have the potential to significantly enhance outcomes and long-term quality of life for those affected by this complex disorder.

4.7. Innovative biomarkers and research questions for future research

EWAS found methylation differences in the TNXB gene between people with AN and HCs (Booij et al. 2015; Kesselmeier et al. 2018; Steiger et al. 2019). These results indicate a crucial role of the structure and stability of connective tissues in the development of AN. Additionally, connective tissue changes were found in the myocardium of patients with severe AN (Lamzabi et al. 2015; Kuwabara et al. 2018; Smythe et al. 2021). Moreover, clinical observations suggest that individuals with connective tissue syndromes manifest with clinical symptoms that overlap with AN, e.g. gastrointestinal problems and lower BMI (Baeza-Velasco et al. 2021). Therefore, future research might elucidate the relationship between abnormal connective tissue and AN, the impact of starvation towards the development of abnormal connective tissue and how the sensory signals sent from potentially abnormal connective tissue to the CNS impact interoception in AN (Gibson and Mehler 2024).

Synaptic biomarkers, crucial for assessing synaptic function and plasticity, have emerged as key players in unravelling the neurobiological underpinnings of neurological disorders. Although studies have suggested alterations in synaptic proteins like synaptophysin, postsynaptic density protein 95 (PSD-95), and SNAP-25 in individuals with various disorders implicating synaptic dysfunction such as dementia (Leuba et al. 2008) there are as yet no studies in AN or other EDs.

Other innovative biological markers could be markers of oxidative stress such as plasma advanced oxidation protein products and advanced glycation end products or activity markers like α4βδ-GABAAR (Aoki et al. 2014). In addition to blood-, saliva-, CSF, urine-, and faeces-based biomarkers, there are breath- or skin-based biomarkers available to reflect on the gastrointestinal, skin or ear-nose-throat microbiome. Rather than relying on a single marker, integrating signal patterns that reflect the status of the brain, appetite regulation, and physical activity may provide greater specificity. However, the use of AI might be necessary to calculate those patterns.

4.7.1. The economics of biomarkers

In addition to the many clinical benefits outlined, the advances in the use of biomarkers in health care present new opportunities in health adjacent disciplines, including epidemiology, health services research, and health economics. Widespread use of biomarker testing will allow for better disease classification and epidemiologic descriptive studies of prevalence or disease progression, as well as predictive modelling (Hay et al. 2023). This knowledge can lead to improved estimations of the burden of disease and associated health care resource needs at the system level (Davillas and Pudney 2020).

Questions remain regarding the economics of biomarker use, specifically the cost-effectiveness of biomarker testing, and the cost-effectiveness of biomarker-guided or pharmacogenetic therapies. Most interesting to health care systems is the question whether reliance on biomarkers and biomarker-guided therapy improves overall health outcomes sufficiently to justify the costs of testing. Studies in this area have focused primarily on oncologic treatments, and we did not identify any cost-effectiveness studies related to biomarkers in AN. Cost-effectiveness research of AN treatments is overall relatively sparce (Faller et al. 2024). In general, the estimation of the cost-effectiveness of biomarker testing is challenging because their impact on health outcomes is indirect and difficult to isolate (Kramer et al. 2025). There is early evidence that biomarker guided treatment has the potential to improve the allocation of resources by improving disease prevention and/or better matching patients with the most appropriate treatments (Verbelen et al. 2017).

4.8. Markers of physical health risk and refeeding markers

Several laboratory markers (e.g. electrolytes, liver enzymes, blood count) are crucial to monitor physical

health and to ensure the safety of people with AN during the refeeding process (Himmerich et al. 2010; Psychiatrists 2022). National clinical and scientific ED societies have established guidance for general and specialised clinicians based on these parameters. Those guidelines like the Medical Emergencies in Eating Disorders (MEED)(Psychiatrists 2022) indicate the physical risk level for patients with AN based on abnormalities of laboratory parameters or results of the physical examination.

Clinicians have also started to develop an overall risk score for underweight patients with AN based on clinically relevant laboratory parameters (Cuntz et al. 2023), and to develop algorithms about how to use these risk parameters to aid diagnostic and therapeutic processes at specific steps during the AN treatment cycle (Himmerich and Treasure 2024). These efforts will hopefully enable clinicians to intervene earlier, to discover and apply more targeted and individually-tailored therapies and to change or escalate treatment where necessary (Himmerich et al. 2024) in order to avoid treatment resistance leading to a chronic course of AN.

4.9. Synopsis

In brief, biomarkers can serve as indicators of the biological vulnerability to AN, reflect its metabolic and psychiatric symptoms, indicate physical health consequences and medical risk, and offer utility in monitoring nutritional, pharmacological or psychotherapeutic treatment strategies. This is summarised in Figure 2. There is no clear-cut distinction between markers related to the metabolic symptoms of AN and markers of its physical health consequences, because the physical health consequences

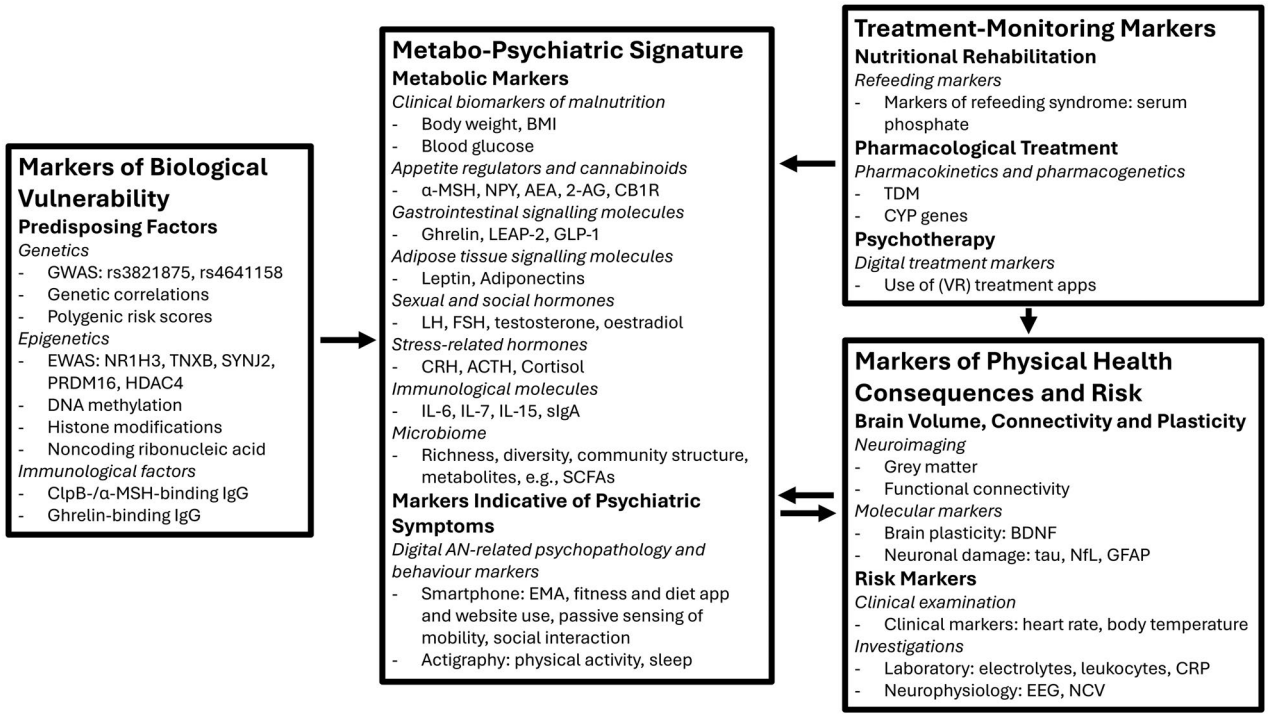

Figure 2. Overview of biological candidate markers of anorexia nervosa. For details see text. The arrows indicate the direction of influence. The markers of biological vulnerability convey the risk for the manifestation of the metabo-psychiatric signature of AN. The metabo-psychiatric markers are involved in the development of the physical health consequences and health risks. Treatment monitoring markers are supposed to aid the treatment which alleviates AN and reduces its biological correlates and health consequences. Abbreviations: α-MSH = α-melanocyte-stimulating hormone; 2-AG = 2-arachidonoylglycerol; ACTH = adrenocorticotropic hormone; AEA = anandamide; AN = anorexia nervosa; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CB1R = Cannabinoid Receptor Type 1; ClpB = caseinolytic protease B; CRH = corticotropin-releasing hormone; CRP = C-reactive protein; CYP = cytochrome P450; DNA = deoxyribonucleic acid; EEG = electroencephalogram; EMA = ecological momentary assessment; EWAS = epigenome-wide association study; FSH = follicle-stimulating hormone; GFAP = glial fibrillary acidic protein; GLP-1 = glucagon-like peptide-1; GWAS = genome-wide association study; HDAC4 = histone deacetylase 4; IgG = immunoglobulin G; IgM = immunoglobulin M; IL = Interleukin; LEAP-2 = liver-expressed antimicrobial peptide 2; LH = luteinizing hormone; NCV = nerve conduction velocity; NfL = neurofilament light chain; NPY = neuropeptide Y; NR1H3 = nuclear receptor subfamily 1 group H member 3; PRDM16 = PR domain containing 16 (protein that tells a precursor cell to turn into a brown fat cell); SCFAs = short-chain fatty acids; sIgA = salivary immunoglobulin A; SYNJ2 = synaptojanin 2; TDM = therapeutic drug monitoring; TNXB = tenascin-X; VR = virtual reality.

of AN – such as GM and functional connectivity loss – perpetuate the illness and worsen its psychiatric and metabolic symptoms. Figure 2 is therefore not meant to visualise clear categories of biological markers but to provide an overview of the various types of biological candidate markers that have been associated with AN.

Alternative categorizations are possible, such as grouping biomarkers into clinical, molecular, cellular, neuroimaging, digital, cardiac, and neurophysiological parameters based on their respective measurement modalities, or into brain, CSF, saliva, plasma, serum or faecal biomarkers according to the location where the sample was taken.

4.10. Limitations

Our consensus statement on biological markers in AN has several limitations. As it focuses on the markers themselves, it did not explain the underpinning pathophysiology. Not all molecules tested in AN could be reported in this consensus paper. Therefore, the task force selected the most promising candidate biomarkers and those with the highest level of evidence. Examples of molecular markers not mentioned in the results section are myostatin which is a myokine that acts as an inhibitor of muscle growth and which has been found to have lower concentrations in the plasma of women with AN compared to controls (Maïmoun et al. 2022) and somatostatin, a polypeptide hormone with numerous inhibitory roles in the body, which, for example, shows a higher plasma level response to a test meal in people with AN compared with HCs and weight-recovered patients with AN (Pirke et al. 1994).

We mainly reported differences between people with AN and HCs. Differences between AN and other disorders associated with low body weight or starvation such as ARFID, constitutional thinness, hyperthyroidism, cancer cachexia, other psychiatric disorders, depression with appetite loss, or schizophrenia with delusion of poisoning were not incorporated into the paper. Similarly, we did not include AAN even though many studies have been unable to find psychological or medical differences in patients of both disorders. This indicates that both disorders represent a single restrictive ED (Golden and Walsh 2024), and a homogenous illness conceptualisation with diagnostic subcategorizations may be more appropriate (Hebebrand, Seitz, et al. 2024). Additionally, AAN has become an increasingly important ED diagnosis in clinical practice. However, biological research into AAN has been scant and unlike AN, which is listed as one of the main Feeding and EDs in, AAN is summarised under OFSED (American Psychiatric Association 2022). Therefore, this consensus paper focused on AN.

Overall, the scientific basis for the biological markers discussed in this article are group comparisons. Studies on the sensitivity, the specificity and the predictive value of these markers for AN are lacking. At present, biomarkers cannot be used as decision aids for diagnosis and treatment. Our review of the literature corroborates the view that currently biological makers only reflect an indication of AN, biological or behavioural features associated with AN, or a physical health risk as a consequence of AN. There are no biological markers available to monitor treatment success or to monitor recovery from physical and mental health consequences. However, TDM might help to increase safety during the pharmacological treatment of AN.

Existing research is not yet at the stage where we can make definitive conclusions about the distinctiveness or the specificity of different biomarkers, or categorise them as risk, diagnosis, trait, state, stage, response or prognosis markers. These are scientific questions for future research in biomarkers of AN.

Acknowledgements

None.

Statement of interest

Hubertus Himmerich, Johanna Louise Keeler, and Janet Treasure report funding from the UK Medical Research Council (MRC) for a double-blinded randomised controlled feasibility trial to test oral ketamine in people with AN and depression. Hubertus Himmerich has been a principal investigator of a proof-of-concept study testing psilocybin in AN; this study was an industry cooperation between the South London and Maudsley NHS Foundation Trust (SLaM), COMPASS Pathfinder Limited and Worldwide Clinical Trials Limited. Andreas Karwautz is vice-president of the scientific network society 'Therapeutic Drug Monitoring in Child and Adolescent Psychiatry, e.V.' based in Würzburg, Germany, and vice-president of the 'Austrian Society on Eating Disorders'. Susan L. McElroy has been a consultant to or member of the scientific advisory boards of Allergan, Avanir, Bracket, F. Hoffmann-La Roche Ltd. Idorsia, Mitsubishi Tanabe Pharma America, Myriad, Novo Nordisk, Opiant, Otsuka, Sipnose, Sunovion and Takeda. She has been a principal or co-investigator on studies sponsored by Allergan, Avanir, Brainsway, Idorsia, Janssen, Marriott Foundation, Medibio, Myriad, National Institute of Mental Health, Neurocrine, Novo Nordisk, Otsuka, and Sunovion. She is also an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent. Michael Berk is supported by a NHMRC Senior Principal Research Fellowship and Leadership 3 Investigator grant (1156072 and 2017131). He received grant funding from Wellcome Trust, MRFF, Victorian Government Department of

Jobs, Precincts and Regions, Cooper University USA, Janssen Lundbeckfonden Copenhagen, St. Biopharma, Psychscene.com, WFSBP, NeuroSAS, CINP, Shanghai Mental Health Centre, Penn State College of Medicine, Precision Psych Fondamental, ISBD, Milken Baszucki Brain Research Fund, Stanley Medical Research Institute, Danmarks Frie Forskningsfond Psykiatrisk Centre Kovenhavn, Patient-Centred Outcomes Research Institute (PCORI), Australian Eating Disorders Research and Translation Centre AEDRTC, USA Department of Defense Office of the Congressionally Directed Medical Research Programs (CDMRP) and Equity Trustees Limited. He received honoraria for lectures from Global Congress of Biological Psychiatry India, Otsuka CNS, RANZCP New Zealand, Eisai Australia, Sandoz, Allori, Lundbeck, World Congress of Psychiatry, African College of Neuropsychopharmacology, SVI Inaugural Health Matters Webinar Series, Argentine Association of Psychiatrists Congress of Psychiatry and Mental Health and Global Bipolar Cohort (GBC). Siegfried Kasper received grants/research support, consulting fees and/or honoraria from Angelini, AOP Orphan Pharmaceuticals AG, Celgene GmbH, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sage, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd., Sun Pharmaceutical Industries Ltd. and Takeda. Fernando Fernandez-Aranda received consultation fees from Novo Nordisk. Philip Gorwood received speaker and advisory board honoraria from Johnson & Johnson, Lundbeck, MindMed and Newron & Otsuka. Johannes Hebebrand received speaker honoraria from Amryt Pharmaceuticals and Novo-Nordisk; he was named as inventor in two patent applications that the University of Duisburg-Essen had filed on the use of leptin analogues for treating anorexia nervosa and atypical anorexia nervosa. All other authors report no conflict of interest.

Funding

Hubertus Himmerich and Janet Treasure receive salary support from the National Institute for Health and Care Research (NIHR) Biomedical Research Centre (BRC) for Mental Health, South London, UK, and Maudsley NHS Foundation Trust and the Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK. Rebecca Morris receives a PhD scholarship from the NIHR Maudsley BRC. Hiba Mutwalli receives a sponsorship from the Saudi Arabian government for higher education. Andreas Karwautz has received salary support from the Medical University of Vienna. Fernando Fernandez-Aranda reports that his contribution was partially supported by the Instituto de Salud Carlos III (FORT23/00032; AC24/00148), AGAUR–Generalitat de Catalunya (2021-SGR-00824), EU Grants (eprObes Ref. 101080219-2 and Biorexia [EPPermed 2024-618]), CIBEROBN which is an initiative of the Instituto de Salud Carlos III (ISCIII), the CERCA Programme/Generalitat de Catalunya for institutional support, und by the Catalan Institution for Research and Advanced Studies (ICREA). This research was additionally supported by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH authors (Dimitrios Kapogiannis) are considered Works of the United States Government. The findings and conclusions expressed in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. Lisa-Katrin Kaufmann was supported by the Swiss National Science Foundation (Grants 202966 and 225519) and by a FAN "Academic Excellence Fellowship" from the University of Zurich.

ORCID

Hubertus Himmerich http://orcid.org/0000-0003-1209-6073
Sabrina Mörkl http://orcid.org/0000-0001-5034-6358
Elżbieta Paszyńska http://orcid.org/0000-0001-7135-6264
Michael Berk http://orcid.org/0000-0002-5554-6946

References

Acres MJ, Heath JJ, Morris JA. 2012. Anorexia nervosa, autoimmunity and the hygiene hypothesis. Med Hypotheses. 78(6):772–775. https://doi.org/10.1016/j.mehy.2012.03.002

Adam TC, Epel ES. 2007. Stress, eating and the reward system. Physiol Behav. 91(4):449–458. https://doi.org/10.1016/j.physbeh.2007.04.011

Affaticati LM et al. 2023. The impact of clinical factors, vitamin b12 and total cholesterol on severity of anorexia nervosa: a multicentric cross-sectional study. Nutrients. 15(23):4954. https://doi.org/10.3390/nu15234954

Afsar B, Afsar RE. 2022. Brain-derived neurotrophic factor (BDNF): a multifaceted marker in chronic kidney disease. Clin Exp Nephrol. 26(12):1149–1159. https://doi.org/10.1007/s10157-022-02268-z

Ahima RS, Bjorbaek C, Osei S, Flier JS. 1999. Regulation of neuronal and glial proteins by leptin: implications for brain development. Endocrinology. 140(6):2755–2762. https://doi.org/10.1210/endo.140.6.6774

Ahima RS et al. 1996. Role of leptin in the neuroendocrine response to fasting. Nature. 382(6588):250–252. https://doi.org/10.1038/382250a0

Ahmed A et al. 2025. A scoping review and hypothetical framework about the interplay between oxytocin and eating disorders. Physiol Behav. 290:114777. https://doi.org/10.1016/j.physbeh.2024.114777

Aira A et al. 2020. Recommendations for stool donor selection for fecal microbiota transplant. Consensus document endorsed by the Catalan Society of Digestology, Catalan Society of Infectious diseases and Clinical microbiology and the GEMBIOTA group from Spanish Society of Infectious Diseases and Clinical Microbiology. Enferm Infecc Microbiol Clin (Engl Ed). (Original work published Recomendaciones para la selección del donante para la transferencia de microbiota fecal. Documento de posicionamiento avalado por la Societat Catalana de Digestologia, la Societat Catalana de Malalties Infeccioses i Microbiologia Clínica y el grupo GEMBIOTA de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica.) https://doi.org/10.1016/j.eimc.2020.09.002

Al Jumaili WA, Jain SB. 2025. Atypical antipsychotic effect on bone mineral density. StatPearls Publishing.

Al Massadi O, Nogueiras R, Dieguez C, Girault JA. 2019. Ghrelin and food reward. Neuropharmacology. 148:131–138. https://doi.org/10.1016/j.neuropharm.2019.01.001

Alberti M et al. 2013. Assessment of physical activity in anorexia nervosa and treatment outcome. Med Sci Sports Exerc. 45(9):1643–1648. https://doi.org/10.1249/MSS.0b013e31828e8f07

Aledavood T et al. 2025. Multimodal digital phenotyping study in patients with major depressive episodes and healthy controls (mobile monitoring of mood): observational longitudinal study. JMIR Ment Health. 12:e63622. https://doi.org/10.2196/63622

Allen AP et al. 2017. The trier social stress test: principles and practice. Neurobiol Stress. 6:113–126. https://doi.org/10.1016/j.ynstr.2016.11.001

Almenara CA, Cimino S, Cerniglia L. 2022. Sensor technology and intelligent systems in anorexia nervosa: providing smarter healthcare delivery systems. Biomed Res Int. 2022(1):1955056. https://doi.org/10.1155/2022/1955056

Anderson EJP et al. 2016. 60 YEARS OF POMC: regulation of feeding and energy homeostasis by α-MSH. J Mol Endocrinol. 56(4):T157–T174. https://doi.org/10.1530/jme-16-0014

Anderson OS, Sant KE, Dolinoy DC. 2012. Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. J Nutr Biochem. 23(8):853–859. https://doi.org/10.1016/j.jnutbio.2012.03.003

Andreani NA et al. 2024. Longitudinal analysis of the gut microbiome in adolescent patients with anorexia nervosa: microbiome-related factors associated with clinical outcome. Gut Microbes. 16(1):2304158. https://doi.org/10.1080/19490976.2024.2304158

Andreoli MF et al. 2024. Pre-prandial plasma liver-expressed antimicrobial peptide 2 (LEAP2) concentration in humans is inversely associated with hunger sensation in a ghrelin independent manner. Eur J Nutr. 63(3):751–762. https://doi.org/10.1007/s00394-023-03304-8

Andries A, Frystyk J, Flyvbjerg A, Støving RK. 2015. Changes in IGF-I, urinary free cortisol and adipokines during dronabinol therapy in anorexia nervosa: results from a randomised, controlled trial. Growth Horm IGF Res. 25(5):247–252. https://doi.org/10.1016/j.ghir.2015.07.006

Antel J et al. 2022. Rapid amelioration of anorexia nervosa in a male adolescent during metreleptin treatment including recovery from hypogonadotropic hypogonadism. Eur Child Adolesc Psychiatry. 31(10):1573–1579. https://doi.org/10.1007/s00787-021-01778-7

Anton-Păduraru DT et al. 2023. The role of the gut microbiota in anorexia nervosa in children and adults-systematic review. Int J Mol Sci. 25(1):41. https://doi.org/10.3390/ijms25010041

Aoki C et al. 2014. α4βδ-GABAARs in the hippocampal CA1 as a biomarker for resilience to activity-based anorexia. Neuroscience. 265:108–123. https://doi.org/10.1016/j.neuroscience.2014.01.011

APA. 2013. Diagnostic and statistical manual of mental disorders: DSM-5™. In: Diagnostic and statistical manual of mental disorders: DSM-5™. 5th ed. American Psychiatric Publishing, Inc. p xliv, 947.

Aperia A, Broberger O, Fohlin L. 1978. Renal function in anorexia nervosa. Acta Paediatr Scand. 67(2):219–224. https://doi.org/10.1111/j.1651-2227.1978.tb16306.x

Arcelus J, Mitchell AJ, Wales J, Nielsen S. 2011. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch Gen Psychiatry. 68(7):724–731. https://doi.org/10.1001/archgenpsychiatry.2011.74

Arold D et al. 2023. Predicting long-term outcome in anorexia nervosa: a machine learning analysis of brain structure at different stages of weight recovery. Psychol Med. 53(16):7827–7836. https://doi.org/10.1017/S0033291723001861

Ascione M et al. 2024. Improving anorexia nervosa treatment with virtual reality body exposure and attentional bias modification: a single case study. Appl Sci. 14(11):4340. https://doi.org/10.3390/app14114340

Assalone C et al. 2022. Determinants of severe bradycardia in adolescents hospitalized for anorexia nervosa. Pediatr Int. 64(1):e14967. https://doi.org/10.1111/ped.14967

American Psychiatric Association. 2022. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association.

Attia E et al. 2019. Olanzapine versus placebo in adult outpatients with anorexia nervosa: a randomized clinical trial. Am J Psychiatry. 176(6):449–456. https://doi.org/10.1176/appi.ajp.2018.18101125.

Bachmann CJ, Haberhausen M, Heinzel-Gutenbrunner M, Remschmidt H, Theisen FM. 2008. Large intraindividual variability of olanzapine serum concentrations in adolescent patients. Ther Drug Monit. 30(1):108–112. https://doi.org/10.1097/FTD.0b013e3181633429

Bacopoulou F et al. 2017. Serum kisspeptin concentrations are negatively correlated with body mass index in adolescents with anorexia nervosa and amenorrhea. Hormones (Athens). 16(1):33–41. https://doi.org/10.14310/horm.2002.1717

Baenas I et al. 2023. Association of anandamide and 2-arachidonoylglycerol concentrations with clinical features and body mass index in eating disorders and obesity. Eur Psychiatry. 66(1):e49. https://doi.org/10.1192/j.eurpsy.2023.2411

Baeza-Velasco C et al. 2021. Gastrointestinal and eating problems in women with Ehlers-Danlos syndromes. Eat Weight Disord. 26(8):2645–2656. https://doi.org/10.1007/s40519-021-01146-z

Baeza-Velasco C. 2021. Neurodevelopmental atypisms in the context of joint hypermobility, hypermobility spectrum disorders, and Ehlers–Danlos syndromes. Am J Med Genet Pt C. 187(4):491–499. https://doi.org/10.1002/ajmg.c.31946

Bahnsen K et al. 2022. Dynamic structural brain changes in anorexia nervosa: a replication study, mega-analysis, and virtual histology approach. J Am Acad Child Adolesc Psychiatry. 61(9):1168–1181. https://doi.org/10.1016/j.jaac.2022.03.026

Bahnsen K et al. 2024. Differential longitudinal changes of hippocampal subfields in patients with anorexia nervosa. Psychiatry Clin Neurosci. 78(3):186–196. https://doi.org/10.1111/pcn.13626

Bailly M et al. 2021a. Underweight but not underfat: is fat-free mass a key factor in constitutionally thin women? Eur J Clin Nutr. 75(12):1764–1770. https://doi.org/10.1038/s41430-021-00895-5

Bailly M et al. 2021b. Is constitutional thinness really different from anorexia nervosa? A systematic review and meta-analysis. Rev Endocr Metab Disord. 22(4):913–971. https://doi.org/10.1007/s11154-021-09650-4.

Ballauff A et al. 1999. Serum leptin and gonadotropin levels in patients with anorexia nervosa during weight gain. Mol Psychiatry. 4(1):71–75. https://doi.org/10.1038/sj.mp.4000478

Bangamuarachchi W et al. 2023. Inferring mood-while-eating with smartphone sensing and community-based model personalization. In: Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies. Vol. *7(2)*.

Baranowska B, Wasilewska-Dziubińska E, Radzikowska M, Płonowski A, Roguski K. 1997. Neuropeptide Y, galanin, and leptin release in obese women and in women with anorexia nervosa. Metabolism. 46(12):1384–1389. https://doi.org/10.1016/s0026-0495(97)90136-0

Baranowska B, Wolinska-Witort E, Wasilewska-Dziubinska E, Roguski K, Chmielowska M. 2001. Plasma leptin, neuropeptide Y (NPY) and galanin concentrations in bulimia nervosa and in anorexia nervosa. Neuro Endocrinol Lett. 22(5):356–358.

Baranowska-Bik A et al. 2017. Adipokine profile in patients with anorexia nervosa. Endokrynol Pol. 68(4):422–429. https://doi.org/10.5603/EP.a2017.0035

Barbier P et al. 2019. Role of Tau as a microtubule-associated protein: structural and functional aspects [review]. Front Aging Neurosci. 11:204. https://doi.org/10.3389/fnagi.2019.00204

Barja-Fernández S et al. 2015. Circulating betatrophin levels are increased in anorexia and decreased in morbidly obese women. J Clin Endocrinol Metab. 100(9):E1188–E1196. https://doi.org/10.1210/JC.2015-1595

Barona M et al. 2019. White matter alterations in anorexia nervosa: evidence from a voxel-based meta-analysis. Neurosci Biobehav Rev. 100:285–295. https://doi.org/10.1016/j.neubiorev.2019.03.002

Barrios V et al. 2024. Reduction in pappalysin-2 levels and lower IGF-I bioavailability in female adolescents with anorexia Nervosa. J Clin Endocrinol Metab. 109(3):e920–e931. https://doi.org/10.1210/clinem/dgad713

Barro C, Chitnis T, Weiner HL. 2020. Blood neurofilament light: a critical review of its application to neurologic disease. Ann Clin Transl Neurol. 7(12):2508–2523. https://doi.org/10.1002/acn3.51234

Bavato F et al. 2024. Introducing neurofilament light chain measure in psychiatry: current evidence, opportunities, and pitfalls. Mol Psychiatry. 29(8):2543–2559. https://doi.org/10.1038/s41380-024-02524-6.

Behrens SC et al. 2023. Virtual reality exposure to a healthy weight body is a promising adjunct treatment for anorexia nervosa. Psychother Psychosom. 92(3):170–179. https://doi.org/10.1159/000530932

Bektas S et al. 2023. Exploring correlations of food-specific disgust with eating disorder psychopathology and food interaction: a preliminary study using virtual reality. Nutrients. 15(20):4443. https://doi.org/10.3390/nu15204443

Bemer P et al. 2021. Bone mineral density at extremely low weight in patients with anorexia nervosa. Clin Endocrinol (Oxf). 95(3):423–429. https://doi.org/10.1111/cen.14498

Berchio C, Annen LC, Bouamoud Y, Micali N. 2023. Temporal dynamics of cognitive flexibility in adolescents with anorexia nervosa: a high-density EEG study. Eur J Neurosci. 57(6):962–980. https://doi.org/10.1111/ejn.15921

Berchio C, Cambi S, Pappaianni E, Micali N. 2022. EEG biomarkers in children and adolescents with feeding and eating disorders: current evidence and future directions. Front Psychiatry. 13:882358. https://doi.org/10.3389/fpsyt.2022.882358

Berchio C, Kumar SS, Micali N. 2024. EEG spatial-temporal dynamics of resting-state activity in young women with anorexia nervosa: preliminary evidence. Brain Topogr. 37(3):447–460. https://doi.org/10.1007/s10548-023-01001-7

Berk M. 2015. The classification of biomarkers. JAMA Psychiatry. 72(10):1056–1057. https://doi.org/10.1001/jamapsychiatry.2015.1113

Bernardoni F et al. 2020. Metabolic state and value-based decision-making in acute and recovered female patients with anorexia nervosa. J Psychiatry Neurosci. 45(4):253–261. https://doi.org/10.1503/jpn.190031.

Bernardoni F et al. 2018. Nutritional status affects cortical folding: lessons learned from anorexia nervosa. Biol Psychiatry. 84(9):692–701. https://doi.org/10.1016/j.biopsych.2018.05.008

Bhargava R et al. 2023. Postprandial increases in liver-gut hormone LEAP2 correlate with attenuated eating behavior in adults without obesity. J Endocr Soc. 7(7):bvad061. https://doi.org/10.1210/jendso/bvad061

Birmingham C, Treasure J. 2019. Medical management of eating disorders. 3rd ed. Cambridge University Press.

Birmingham CL et al. 2003. Reduced febrile response to bacterial infection in anorexia nervosa patients. Int J Eat Disord. 34(2):269–272. https://doi.org/10.1002/eat.10189

Boehm I et al. 2016. Partially restored resting-state functional connectivity in women recovered from anorexia nervosa. J Psychiatry Neurosci. 41(6):377–385. https://doi.org/10.1503/jpn.150259

Bomba M et al. 2018. QT interval and dispersion in drug-free anorexia nervosa adolescents: a case control study. Eur Child Adolesc Psychiatry. 27(7):861–866. https://doi.org/10.1007/s00787-017-1080-1

Booij L et al. 2015. DNA methylation in individuals with anorexia nervosa and in matched normal-eater controls: a genome-wide study. Int J Eat Disord. 48(7):874–882. https://doi.org/10.1002/eat.22374

Booij L, Steiger H. 2020. Applying epigenetic science to the understanding of eating disorders: a promising paradigm for research and practice. Curr Opin Psychiatry. 33(6):515–520. https://doi.org/10.1097/YCO.0000000000000632

Boraska V et al. 2012. Genome-wide association analysis of eating disorder-related symptoms, behaviors, and personality traits. Am J Med Genet B Neuropsychiatr Genet. 159B(7):803–811. https://doi.org/10.1002/ajmg.b.32087

Boraska V et al. 2014. A genome-wide association study of anorexia nervosa. Mol Psychiatry. 19(10):1085–1094. https://doi.org/10.1038/mp.2013.187

Borgia F et al. 2021. Anorexia nervosa-related cardiopathy in children with physical instability: prevalence, echocardiographic characteristics and reversibility at mid-term follow-up. Eur J Pediatr. 180(11):3379–3389. https://doi.org/10.1007/s00431-021-04130-y

Borgo F et al. 2017. Microbiota in anorexia nervosa: the triangle between bacterial species, metabolites and psychological tests. PLoS One. 12(6):e0179739. https://doi.org/10.1371/journal.pone.0179739.

Borsdorf B et al. 2021. BDNF levels in adolescent patients with anorexia nervosa increase continuously to supranormal levels 2.5 years after first hospitalization. J Psychiatry Neurosci. 46(5):E568–e578. https://doi.org/10.1503/jpn.210049

Bou Khalil R et al. 2022. Neutrophil-to-lymphocyte ratio (NLR) variations in relationship with childhood maltreatment in patients with anorexia nervosa: a retrospective cohort study. Eat Weight Disord. 27(6):2201–2212. https://doi.org/10.1007/s40519-022-01372-z

Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P. 2012. Anorexia nervosa and the kidney. Am J Kidney Dis. 60(2):299–307. https://doi.org/10.1053/j.ajkd.2012.03.019

Bouret SG. 2010. Neurodevelopmental actions of leptin. Brain Res. 1350:2–9. https://doi.org/10.1016/j.brainres.2010.04.011
Bowers TK, Eckert E. 1978. Leukopenia in anorexia nervosa: lack of increased risk of infection. Arch Intern Med. 138(10):1520–1523. https://doi.org/10.1001/archinte.1978.03630350050015
Boyd ED, Durant NH. 2018. Recurrent hyponatremia in a young adult woman with anorexia nervosa and the effects of insufficient communication. Int J Eat Disord. 51(12):1378–1381. https://doi.org/10.1002/eat.22973
Bracké KFM et al. 2023. Can neuroimaging measures differentiate the disease course of anorexia nervosa? A systematic review. J Psychiatr Res. 163:337–349. https://doi.org/10.1016/j.jpsychires.2023.05.059
Brandtzaeg P. 2007. Do salivary antibodies reliably reflect both mucosal and systemic immunity? Ann N Y Acad Sci. 1098(1):288–311. https://doi.org/10.1196/annals.1384.012
Brandys MK, Kas MJ, Van Elburg AA, Campbell IC, Adan RA. 2011. A meta-analysis of circulating BDNF concentrations in anorexia nervosa. World J Biol Psychiatry. 12(6):444–454. https://doi.org/10.3109/15622975.2011.562244
Brandys MK et al. 2013. The Val66Met polymorphism of the BDNF gene in anorexia nervosa: new data and a meta-analysis. World J Biol Psychiatry. 14(6):441–451. https://doi.org/10.3109/15622975.2011.605470
Breithaupt L et al. 2024. Identification of state markers in anorexia nervosa: replication and extension of inflammation-associated biomarkers using multiplex profiling. Biol Psychiatry Glob Open Sci. 4(5):100332. https://doi.org/10.1016/j.bpsgos.2024.100332
Brennan C et al. 2024. Greater rate of weight loss predicts paediatric hospital admission in adolescent typical and atypical anorexia nervosa. Eur J Pediatr. 183(4):1789–1799. https://doi.org/10.1007/s00431-024-05436-3
Brennan C, Illingworth S, Cini E, Bhakta D. 2023. Medical instability in typical and atypical adolescent anorexia nervosa: a systematic review and meta-analysis. J Eat Disord. 11(1):58. https://doi.org/10.1186/s40337-023-00779-y
Brizzi G et al. 2025. Therapeutic immersion: a single-subject study on virtual reality multisensory experiences for mitigating body disturbance in anorexia nervosa. Eat Weight Disord. 30(1):1–7. https://doi.org/10.1007/s40519-025-01740-5
Bronsky J et al. 2011. Changes of orexin A plasma levels in girls with anorexia nervosa during eight weeks of realimentation. Int J Eat Disord. 44(6):547–552. https://doi.org/10.1002/eat.20857
Brown RF, Bartrop R, Beumont P, Birmingham CL. 2005. Bacterial infections in anorexia nervosa: delayed recognition increases complications. Int J Eat Disord. 37(3):261–265. https://doi.org/10.1002/eat.20135
Brunoni AR, Lopes M, Fregni F. 2008. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol. 11(8):1169–1180. https://doi.org/10.1017/S1461145708009309
Buck P, Joli J, Zipfel S, Stengel A. 2022. Carbohydrate malabsorption in anorexia nervosa: a systematic review. J Eat Disord. 10(1):189. https://doi.org/10.1186/s40337-022-00713-8
Bulant J et al. 2020. Changes of BMI, steroid metabolome and psychopathology in patients with anorexia nervosa during hospitalization. Steroids. 153:108523. https://doi.org/10.1016/j.steroids.2019.108523
Bulik CM. 2024. Building confidence in discussing genetics with patients with eating disorders and their families. Focus (Am Psychiatr Publ). 22(3):322–327. https://doi.org/10.1176/appi.focus.20230040.
Bulik CM, Blake L, Austin J. 2019. Genetics of eating disorders: what the clinician needs to know. Psychiatr Clin North Am. 42(1):59–73. https://doi.org/10.1016/j.psc.2018.10.007
Bulik CM, Carroll IM, Mehler P. 2021. Reframing anorexia nervosa as a metabo-psychiatric disorder. Trends Endocrinol Metab. 32(10):752–761. https://doi.org/10.1016/j.tem.2021.07.010
Bulik CM et al. 2023. ARFID Genes and Environment (ARFID-GEN): study protocol. BMC Psychiatry. 23(1):863. https://doi.org/10.1186/s12888-023-05266-x
Bulik CM et al. 2021. The eating disorders genetics initiative (EDGI): study protocol. BMC Psychiatry. 21(1):234. https://doi.org/10.1186/s12888-021-03212-3
Bulik-Sullivan B et al. 2015. An atlas of genetic correlations across human diseases and traits. Nat Genet. 47(11):1236–1241. https://doi.org/10.1038/ng.3406.
Burdo J et al. 2020. Plasma levels of one-carbon metabolism nutrients in women with anorexia nervosa. Int J Eat Disord. 53(9):1534–1538. https://doi.org/10.1002/eat.23292.
Burstein D et al. 2023. Genome-wide analysis of a model-derived binge eating disorder phenotype identifies risk loci and implicates iron metabolism. Nat Genet. 55(9):1462–1470. https://doi.org/10.1038/s41588-023-01464-1
Caldiroli A et al. 2023. Clinical and peripheral biomarkers in female patients affected by anorexia: Does the neutrophil/lymphocyte ratio (NLR) affect severity? Nutrients. 15(5):1133. https://doi.org/10.3390/nu15051133
Califf RM. 2018. Biomarker definitions and their applications. Exp Biol Med (Maywood). 243(3):213–221. https://doi.org/10.1177/1535370217750088
Calikoglu B et al. 2024. Effects of weight intervention-induced changes in pathological fat mass of patients with extreme obesity and anorexia nervosa on adipokines and visceral adipocyte functions: a prospective, comparative, observational study. Eur Rev Med Pharmacol Sci. 28(4):1439–1455. https://doi.org/10.26355/eurrev_202402_35474
Campbell IC, Mill J, Uher R, Schmidt U. 2011. Eating disorders, gene–environment interactions and epigenetics. Neurosci Biobehav Rev. 35(3):784–793. https://doi.org/10.1016/j.neubiorev.2010.09.012
Canalis E. 1996. Clinical review 83: mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. J Clin Endocrinol Metab. 81(10):3441–3447. https://doi.org/10.1210/jcem.81.10.8855781
Cao J, Gorwood P, Ramoz N, Viltart O. 2024. The role of central and peripheral brain-derived neurotrophic factor (BDNF) as a biomarker of anorexia nervosa reconceptualized as a metabo-psychiatric disorder. Nutrients. 16(16):2617. https://doi.org/10.3390/nu16162617
Casper RC. 1996. Carbohydrate metabolism and its regulatory hormones in anorexia nervosa. Psychiatry Res. 62(1):85–96. https://doi.org/10.1016/0165-1781(96)02984-8
Casper RC, Kirschner B, Sandstead HH, Jacob RA, Davis JM. 1980. An evaluation of trace metals, vitamins, and taste function in anorexia nervosa. Am J Clin Nutr. 33(8):1801–1808. https://doi.org/10.1093/ajcn/33.8.1801
Cassioli E et al. 2025. Leptin levels in acute and recovered eating disorders: an arm-based network meta-analysis. Eur

Eat Disord Rev. 33(3):525–537. https://doi.org/10.1002/erv.3163
Castellini G et al. 2023. Gut microbiota metabolites mediate the interplay between childhood maltreatment and psychopathology in patients with eating disorders. Sci Rep. 13(1):11753. https://doi.org/10.1038/s41598-023-38665-x
Castellini G, Lelli L, Ricca V, Maggi M. 2016. Sexuality in eating disorders patients: etiological factors, sexual dysfunction and identity issues. A systematic review. Horm Mol Biol Clin Investig. 25(2):71–90. https://doi.org/10.1515/hmbci-2015-0055
Castro J, Deulofeu R, Gila A, Puig J, Toro J. 2004. Persistence of nutritional deficiencies after short-term weight recovery in adolescents with anorexia nervosa. Int J Eat Disord. 35(2):169–178. https://doi.org/10.1002/eat.10249
Cha J et al. 2016. Abnormal reward circuitry in anorexia nervosa: a longitudinal, multimodal MRI study. Hum Brain Mapp. 37(11):3835–3846. https://doi.org/10.1002/hbm.23279
Challier P, Cabrol S. 1995. [Severe hyponatremia associated with anorexia nervosa: role of inappropriate antidiuretic hormone secretion?]. Arch Pediatr. 2(10):977–979. https://doi.org/10.1016/0929-693x(96)89894-0 (Original work published Hyponatrémie sévère associée à une anorexie mentale: rôle d'une sécrétion inappropriée d'hormone antidiurétique?)
Chambers ES et al. 2015. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut. 64(11):1744–1754. https://doi.org/10.1136/gutjnl-2014-307913
Chan JC, Nugent BM, Bale TL. 2018. Parental advisory: maternal and paternal stress can impact offspring neurodevelopment. Biol Psychiatry. 83(10):886–894. https://doi.org/10.1016/j.biopsych.2017.10.005
Chang Y-J, Yen Y-C. 2010. Cytokines and major psychiatric disorders. Taiwanese J Psychiatry. 24(4):257–268. https://doi.org/10.4103/tpsy.tpsy_26_23
Chang X et al. 2019. Microduplications at the 15q11.2 BP1-BP2 locus are enriched in patients with anorexia nervosa. J Psychiatr Res. 113:34–38. https://doi.org/10.1016/j.jpsychires.2019.01.021
Charney DS et al. 2002. Neuroscience research agenda to guide development of a pathophysiologically based classification system.
Che Mokhtar M et al. 2022. Severe hyponatraemia secondary to psychogenic polydipsia in a patient with anorexia nervosa. J Paediatr Child Health. 58(7):1267–1269. https://doi.org/10.1111/jpc.15820
Chen C-Y, Chiang Y-C, Kuo T-C, Tam K-W, Loh E-W. 2021. Effects of intranasal oxytocin in food intake and craving: a meta-analysis of clinical trials. Clin Nutr. 40(10):5407–5416. https://doi.org/10.1016/j.clnu.2021.08.011
Chen L, Liu Z, Zheng Y. 2023. Acute liver failure and aplastic crisis due to anorexia nervosa in an adolescent girl: a case report. J Int Med Res. 51(11):3000605231214922. https://doi.org/10.1177/03000605231214922
Chen X et al. 2021. Resting-state functional network connectivity underlying eating disorder symptoms in healthy young adults. Neuroimage Clin. 30:102671. https://doi.org/10.1016/j.nicl.2021.102671
Cheng Z et al. 2005. A genome-wide comparison of recent chimpanzee and human segmental duplications. Nature. 437(7055):88–93. https://doi.org/10.1038/nature04000
Cho M, Park D, Choo M, Kim J, Han DH. 2024. Development and initial evaluation of a digital phenotype collection system for adolescents: proof-of-concept study. JMIR Form Res. 8:e59623. https://doi.org/10.2196/59623
Cleary BS, Gaudiani JL, Mehler PS. 2010. Interpreting the complete blood count in anorexia nervosa. Eat Disord. 18(2):132–139. https://doi.org/10.1080/10640260903585540
Collantoni E et al. 2020. Cortical complexity in anorexia nervosa: a fractal dimension analysis. J Clin Med. 9(3) https://doi.org/10.3390/jcm9030833
Collantoni E et al. 2025. Cortical complexity in eating disorders: a systematic review and qualitative synthesis. Eur Arch Psychiatry Clin Neurosci. 1–16. https://doi.org/10.1007/s00406-025-02001-3
Considine RV et al. 1996. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 334(5):292–295. https://doi.org/10.1056/nejm199602013340503
Cooke RA et al. 1994. QT interval in anorexia nervosa. Br Heart J. 72(1):69–73. https://doi.org/10.1136/hrt.72.1.69
Copeland PM. 1989. Diuretic abuse and central pontine myelinolysis. Psychother Psychosom. 52(1–3):101–105. https://doi.org/10.1159/000288307.
Cost J, Krantz MJ, Mehler PS. 2020. Medical complications of anorexia nervosa. Cleve Clin J Med. 87(6):361–366. https://doi.org/10.3949/ccjm.87a.19084
Cowdrey FA, Filippini N, Park RJ, Smith SM, McCabe C. 2014. Increased resting state functional connectivity in the default mode network in recovered anorexia nervosa. Hum Brain Mapp. 35(2):483–491. https://doi.org/10.1002/hbm.22202
Culbert KM, Racine SE, Klump KL. 2016. Hormonal factors and disturbances in eating disorders. Curr Psychiatry Rep. 18(7):65. https://doi.org/10.1007/s11920-016-0701-6
Cummings JL et al. 2025. Biomarker-guided decision making in clinical drug development for neurodegenerative disorders. Nat Rev Drug Discov. 24(8):589–609. https://doi.org/10.1038/s41573-025-01165-w.
Cuntz U, Körner T, Voderholzer U. 2022. Rapid renutrition improves health status in severely malnourished inpatients with AN - score-based evaluation of a high caloric refeeding protocol in severely malnourished inpatients with anorexia nervosa in an intermediate care unit. Eur Eat Disord Rev. 30(2):178–189. https://doi.org/10.1002/erv.2877.
Cuntz U, Quadflieg N, Voderholzer U. 2023. Health risk and underweight. Nutrients. 15(14):3262. https://doi.org/10.3390/nu15143262
Cuntz U, Voderholzer U. 2022. Liver damage is related to the degree of being underweight in anorexia nervosa and improves rapidly with weight gain. Nutrients. 14(12):2378. https://doi.org/10.3390/nu14122378
Curtis M et al. 2024. Anorexia nervosa polygenic risk, beyond diagnoses: relationship with adolescent disordered eating and behaviors in an Australian female twin population. Psychol Med. 54(13):1–9. https://doi.org/10.1017/S0033291724001727
Cussen A, Harding A. 2021. Improvement of atrioventricular block with weight restoration in an adolescent with anorexia nervosa. J Paediatr Child Health. 57(12):2001–2004. https://doi.org/10.1111/jpc.15393
D'Addario C et al. 2014. Endocannabinoid signaling and food addiction. Neurosci Biobehav Rev. 47:203–224. https://doi.org/10.1016/j.neubiorev.2014.08.008

D'mello SK, Kory J. 2015. A review and meta-analysis of multimodal affect detection systems. ACM Comput Surv. 47(3) Article:1–36. https://doi.org/10.1145/2682899

da Silva JSV et al. 2020. ASPEN consensus recommendations for refeeding syndrome. Nutr Clin Pract. 35(2):178–195. https://doi.org/10.1002/ncp.10474

Dalton B et al. 2018. A meta-analysis of cytokine concentrations in eating disorders. J Psychiatr Res. 103:252–264. https://doi.org/10.1016/j.jpsychires.2018.06.002

Davillas A, Pudney S. 2020. Using biomarkers to predict healthcare costs: evidence from a UK household panel. J Health Econ. 73:102356. https://doi.org/10.1016/j.jhealeco.2020.102356

Davis C et al. 2024. Prevalence and risk factors associated with low bone mineral density in Asian adolescents with anorexia nervosa and atypical anorexia nervosa. Int J Eat Disord. 57(4):819–826. https://doi.org/10.1002/eat.24076

Davis J et al. 2015. Towards a classification of biomarkers of neuropsychiatric disease: from encompass to compass. Mol Psychiatry. 20(2):152–153. https://doi.org/10.1038/mp.2014.139

de Clercq NC, Frissen MN, Davids M, Groen AK, Nieuwdorp M. 2019. Weight gain after fecal microbiota transplantation in a patient with recurrent underweight following clinical recovery from anorexia nervosa. Psychother Psychosom. 88(1):58–60. https://doi.org/10.1159/000495044

De Kloet ER, Vreugdenhil E, Oitzl MS, Joëls M. 1998. Brain corticosteroid receptor balance in health and disease. Endocr Rev. 19(3):269–301. https://doi.org/10.1210/edrv.19.3.0331

de Reus AJ et al. 2024. GFAP-isoforms in the nervous system: understanding the need for diversity. Curr Opin Cell Biol. 87:102340. https://doi.org/10.1016/j.ceb.2024.102340

de Rijk ESJ et al. 2024. An overview and investigation of relapse predictors in anorexia nervosa: a systematic review and meta-analysis. Int J Eat Disord. 57(1):3–26. https://doi.org/10.1002/eat.24059

de Rosa D et al. 1983. Endocrine study of anorexia nervosa. Exp Clin Endocrinol. 82(2):160–172. https://doi.org/10.1055/s-0029-1210272

de Zwaan M, Aslam Z, Mitchell JE. 2002. Research on energy expenditure in individuals with eating disorders: a review. Int J Eat Disord. 32(2):127–134. https://doi.org/10.1002/eat.10074

Denburg MR et al. 2017. Risk of urolithiasis in anorexia nervosa: a population-based cohort study using the health improvement network. Eur Eat Disord Rev. 25(5):406–410. https://doi.org/10.1002/erv.2526

Depaoli A, Long A, Fine GM, Stewart M, O'Rahilly S. 2018. Efficacy of metreleptin for weight loss in overweight and obese adults with low leptin levels. Diabetes. 67(Supplement_1):296. LBhttps://doi.org/10.2337/db18-296-LB

Di Lodovico L et al. 2021. Anorexia nervosa and gut microbiota: a systematic review and quantitative synthesis of pooled microbiological data. Prog Neuropsychopharmacol Biol Psychiatry. 106:110114. https://doi.org/10.1016/j.pnpbp.2020.110114

Díaz-Marsá M, Alberdi-Páramo I, Niell-Galmés L. 2017. Nutritional supplements in eating disorders. Actas Esp Psiquiatr. 45(Supplement):26–36.

Diaz-Perdigones, C., Moreno-Indias, I., Aguera, Z., Baenas, I., Camacho, L., Subiri, A., Jimenez-Murcia, S., Tinahones, F. J., & Fernandez-Aranda, F. (Submitted). Oral microbiota as a biological marker of self-induced vomiting behaviour in eating disorders.

Dick DM, Riley B, Kendler KS. 2010. Nature and nurture in neuropsychiatric genetics: where do we stand? Dialogues Clin Neurosci. 12(1):7–23. https://doi.org/10.31887/DCNS.2010.12.1/ddick.

Dinkler L et al. 2023. Etiology of the broad avoidant restrictive food intake disorder phenotype in Swedish twins aged 6 to 12 years. JAMA Psychiatry. 80(3):260–269. https://doi.org/10.1001/jamapsychiatry.2022.4612

DiPatrizio NV. 2014. Is fat taste ready for primetime? Physiol Behav. 136:145–154. https://doi.org/10.1016/j.physbeh.2014.03.002

Dive A, Donckier J, Lejeune D, Buysschaert M. 1991. Hypokalemic rhabdomyolysis in anorexia nervosa. Acta Neurol Scand. 83(6):419–419. https://doi.org/10.1111/j.1600-0404.1991.tb03976.x

Docx MK et al. 2010. Pericardial effusions in adolescent girls with anorexia nervosa: clinical course and risk factors. Eat Disord. 18(3):218–225. https://doi.org/10.1080/10640261003719484.

Doose A et al. 2022. Neural and glial damage markers in women after long-term weight-recovery from anorexia nervosa. Psychoneuroendocrinology. 135:105576. https://doi.org/10.1016/j.psyneuen.2021.105576.

Doose A et al. 2023. Triangulating brain alterations in anorexia nervosa: a multimodal investigation of magnetic resonance spectroscopy, morphometry and blood-based biomarkers. Transl Psychiatry. 13(1):277. https://doi.org/10.1038/s41398-023-02580-6

Dostalova I, Kunesova M, Duskova J, Papezova H, Nedvidkova J. 2006. Adipose tissue resistin levels in patients with anorexia nervosa. Nutrition. 22(10):977–983. https://doi.org/10.1016/j.nut.2006.06.006

Dostálová I, Sedláčková D, Papežová H, Nedvídková J, Haluzík M. 2009. Serum visfatin levels in patients with anorexia nervosa and bulimia nervosa. Physiol Res. 58(6):903–907. https://doi.org/10.33549/physiolres.931680

Dowlati Y et al. 2010. A meta-analysis of cytokines in major depression. Biol Psychiatry. 67(5):446–457. https://doi.org/10.1016/j.biopsych.2009.09.033

Dowman J, Arulraj R, Chesner I. 2010. Recurrent acute hepatic dysfunction in severe anorexia nervosa. Int J Eat Disord. 43(8):770–772. https://doi.org/10.1002/eat.20775

Drexl K et al. 2025. Readdressing the ongoing challenge of missing data in youth ecological momentary assessment studies: meta-analysis update. J Med Internet Res. 27:e65710. https://doi.org/10.2196/65710

Du Montcel CT et al. 2023. The role of dysregulated ghrelin/LEAP-2 balance in anorexia nervosa. iScience. 26(11):107996.

Dulewicz M et al. 2022. Biomarkers for the diagnosis of Alzheimer's disease in clinical practice: the role of CSF biomarkers during the evolution of diagnostic criteria. Int J Mol Sci. 23(15):8598. https://doi.org/10.3390/ijms23158598

Duncan L et al. 2017. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. Am J Psychiatry. 174(9):850–858. https://doi.org/10.1176/appi.ajp.2017.16121402

Duriez P et al. 2020. Unexpected association of desacyl-ghrelin with physical activity and chronic food restriction: a translational study on anorexia nervosa. J Clin Med. 9(9):2782. https://doi.org/10.3390/jcm9092782

Dutkiewicz A et al. 2022. Ghrelin and obestatin in adolescent patients with anorexia nervosa: is there an association with

disordered eating, depression, and obsessive-compulsive symptoms? Psychiatry Int. 3(3):248–263. https://doi.org/10.3390/psychiatryint3030020

Eap CB et al. 2021. Tools for optimising pharmacotherapy in psychiatry (therapeutic drug monitoring, molecular brain imaging and pharmacogenetic tests): focus on antidepressants. World J Biol Psychiatry. 22(8):561–628. https://doi.org/10.1080/15622975.2021.1878427

Edgar RD, Jones MJ, Meaney MJ, Turecki G, Kobor MS. 2017. BECon: a tool for interpreting DNA methylation findings from blood in the context of brain. Transl Psychiatry. 7(8):e1187–e1187–e1187. https://doi.org/10.1038/tp.2017.171.

Egberts K et al. 2015. [Pharmacovigilance in child and adolescent psychiatry]. Z Kinder Jugendpsychiatr Psychother. 43(1):21–28. https://doi.org/10.1024/1422-4917/a000329. (Original work published Pharmakovigilanz in der kinder- und jugendpsychiatrie.)

Egberts K et al. 2020. Therapeutic drug monitoring of children and adolescents treated with aripiprazole: observational results from routine patient care. J Neural Transm (Vienna). 127(12):1663–1674. https://doi.org/10.1007/s00702-020-02253-4.

Egberts KM et al. 2022. Serious adverse drug reactions in children and adolescents treated on- and off-label with antidepressants and antipsychotics in clinical practice. Pharmacopsychiatry. 55(5):255–265. https://doi.org/10.1055/a-1716-1856.

Ehrlich S et al. 2015. Reduced functional connectivity in the thalamo-insular subnetwork in patients with acute anorexia nervosa. Hum Brain Mapp. 36(5):1772–1781. https://doi.org/10.1002/hbm.22736

Ehrlich S, Querfeld U, Pfeiffer E. 2006. Refeeding oedema : an important complication in the treatment of anorexia nervosa. Eur Child Adolesc Psychiatry. 15(4):241–243. https://doi.org/10.1007/s00787-006-0528-5.

Eichin KN, Georgii C, Schnepper R, Voderholzer U, Blechert J. 2023. Emotional food-cue-reactivity in anorexia nervosa and bulimia nervosa: an electroencephalography study. Int J Eat Disord. 56(11):2096–2106. https://doi.org/10.1002/eat.24028

El Ghoch M, Calugi S, Dalle Grave R. 2016. Management of severe rhabdomyolysis and exercise-associated hyponatremia in a female with anorexia nervosa and excessive compulsive exercising. Case Rep Med. 2016:8194160–8194165. https://doi.org/10.1155/2016/8194160

Escelsior A et al. 2022. Anti-hypothalamus autoantibodies in anorexia nervosa: a possible new mechanism in neuro-physiological derangement? Eat Weight Disord. 27(7):2481–2496. https://doi.org/10.1007/s40519-022-01388-5

Espinoza-García AS et al. 2022. IgG antibodies reacting with ghrelin and leptin are correlated with body composition and appetitive traits in young subjects. Appetite. 168:105685. https://doi.org/10.1016/j.appet.2021.105685

Fairburn CG, Rothwell ER. 2015. Apps and eating disorders: a systematic clinical appraisal. Int J Eat Disord. 48(7):1038–1046. https://doi.org/10.1002/eat.22398

Fairweather-Schmidt AK, Wade TD. 2015. Changes in genetic and environmental influences on disordered eating between early and late adolescence: a longitudinal twin study. Psychol Med. 45(15):3249–3258. https://doi.org/10.1017/S0033291715001257

Fairweather-Schmidt AK, Wade TD. 2017. Weight-related peer-teasing moderates genetic and environmental risk and disordered eating: twin study. Br J Psychiatry. 210(5):350–355. https://doi.org/10.1192/bjp.bp.116.184648.

Faller J et al. 2024. Economic evidence for prevention and treatment of eating disorders: an updated systematic review. Int J Eat Disord. 57(2):265–285. https://doi.org/10.1002/eat.24113

Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. 1997. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature. 385(6612):165–168. https://doi.org/10.1038/385165a0

Fan Y et al. 2023. The gut microbiota contributes to the pathogenesis of anorexia nervosa in humans and mice. Nat Microbiol. 8(5):787–802. https://doi.org/10.1038/s41564-023-01355-5

Farooqi IS, O'Rahilly S. 2009. Leptin: a pivotal regulator of human energy homeostasis. Am J Clin Nutr. 89(3):980s–984s. https://doi.org/10.3945/ajcn.2008.26788C

Favaro A, Caregaro L, Burlina AB, Santonastaso P. 2000. Tryptophan levels, excessive exercise, and nutritional status in anorexia nervosa. Psychosom Med. 62(4):535–538. https://doi.org/10.1097/00006842-200007000-00012

Favaro A et al. 2012. Disruption of visuospatial and somatosensory functional connectivity in anorexia nervosa. Biol Psychiatry. 72(10):864–870. https://doi.org/10.1016/j.biopsych.2012.04.025

Fazeli PK et al. 2019. Changes in marrow adipose tissue with short-term changes in weight in premenopausal women with anorexia nervosa. Eur J Endocrinol. 180(3):189–199. https://doi.org/10.1530/eje-18-0824

Fazeli PK, Klibanski A. 2014. Anorexia nervosa and bone metabolism. Bone. 66:39–45. https://doi.org/10.1016/j.bone.2014.05.014

Fazeli PK, Klibanski A. 2018. Effects of anorexia nervosa on bone metabolism. Endocr Rev. 39(6):895–910. https://doi.org/10.1210/er.2018-00063

FDA-NIH Biomarker Working Group. 2016. BEST (Biomarkers, EndpointS, and other Tools) Resource. National Institutes of Health (US).

Fekete S, Hiemke C, Gerlach M. 2020. Dose-related concentrations of neuroactive/psychoactive drugs expected in blood of children and adolescents. Ther Drug Monit. 42(2):315–324. https://doi.org/10.1097/ftd.0000000000000685.

Fekete S et al. 2017. Therapeutic drug monitoring in children and adolescents under pharmacotherapy with olanzapine in daily clinical practice. Ther Drug Monit. 39(3):273–281. https://doi.org/10.1097/ftd.0000000000000398

Fernández-Aranda F et al. 2016. Smell–taste dysfunctions in extreme weight/eating conditions: analysis of hormonal and psychological interactions. Endocrine. 51(2):256–267. https://doi.org/10.1007/s12020-015-0684-9

Ferreira AC, Osório FL. 2022. Peripheral oxytocin concentrations in psychiatric disorders - A systematic review and methanalysis: further evidence. Prog Neuropsychopharmacol Biol Psychiatry. 117:110561. https://doi.org/10.1016/j.pnpbp.2022.110561

Fetissov SO et al. 2002. Autoantibodies against α-MSH, ACTH, and LHRH in anorexia and bulimia nervosa patients. Proc Natl Acad Sci U S A. 99(26):17155–17160. https://doi.org/10.1073/pnas.222658699

Fetissov SO et al. 2005. Autoantibodies against neuropeptides are associated with psychological traits in eating disorders. Proc Natl Acad Sci U S A. 102(41):14865–14870. https://doi.org/10.1073/pnas.0507204102

Fetissov SO, Hökfelt T. 2019. On the origin of eating disorders: altered signaling between gut microbiota, adaptive immunity and the brain melanocortin system regulating feeding behavior. Curr Opin Pharmacol. 48:82–91. https://doi.org/10.1016/j.coph.2019.07.004

Fichter MM, Doerr P, Pirke KM, Lund R. 1982. Behavior, attitude, nutrition and endocrinology in anorexia nervosa. Acta Psychiatr Scand. 66(6):429–444. https://doi.org/10.1111/j.1600-0447.1982.tb04500.x

Fichter MM, Pirke K-M, Holsboer F. 1986. Weight loss causes neuroendocrine disturbances: experimental study in healthy starving subjects. Psychiatry Res. 17 doi:(1):61–72. https://doi.org/10.1016/0165-1781(86)90042-9]

Fisher M, Gonzalez M, Malizio J. 2015. Eating disorders in adolescents: how does the DSM-5 change the diagnosis? Int J Adolesc Med Health. 27(4):437–441. https://doi.org/10.1515/ijamh-2014-0059

Flier JS, Maratos-Flier E. 2017. Leptin's physiologic role: does the emperor of energy balance have no clothes? Cell Metab. 26(1):24–26. https://doi.org/10.1016/j.cmet.2017.05.013

Föcker M et al. 2020. Evaluation of metabolic profiles of patients with anorexia nervosa at inpatient admission, short- and long-term weight regain-descriptive and pattern analysis. Metabolites. 11(1):7. https://doi.org/10.3390/metabo11010007.

Föcker M et al. 2011. Screening for anorexia nervosa via measurement of serum leptin levels. J Neural Transm (Vienna). 118(4):571–578. https://doi.org/10.1007/s00702-010-0551-z.

Föcker M et al. 2012. Comparison of metabolic profiles of acutely ill and short-term weight recovered patients with anorexia nervosa reveals alterations of 33 out of 163 metabolites. J Psychiatr Res. 46(12):1600–1609. https://doi.org/10.1016/j.jpsychires.2012.08.015

Fortune RS, Kaplan DW. 2012. Leg swelling a patient with anorexia nervosa. Adolesc Med State Art Rev. 23(2):266–270.

Frey M et al. 2023. Therapeutic drug monitoring in children and adolescents: findings on fluoxetine from the TDM-VIGIL trial. Pharmaceutics. 15(9):2202. https://doi.org/10.3390/pharmaceutics15092202

Friedman JM. 2019. Leptin and the endocrine control of energy balance. Nat Metab. 1(8):754–764. https://doi.org/10.1038/s42255-019-0095-y.

Frølich J et al. 2020a. Assessment of fracture risk in women with eating disorders: the utility of dual-energy x-ray absorptiometry (DXA)-Clinical cohort study. Int J Eat Disord. 53(4):595–605. https://doi.org/10.1002/eat.23245.

Frølich J et al. 2020b. Fractures in women with eating disorders-Incidence, predictive factors, and the impact of disease remission: cohort study with background population controls. Int J Eat Disord. 53(7):1080–1087. https://doi.org/10.1002/eat.23223

Fu W, O'Connor TD, Akey JM. 2013. Genetic architecture of quantitative traits and complex diseases. Curr Opin Genet Dev. 23(6):678–683. https://doi.org/10.1016/j.gde.2013.10.008

Fujimoto S et al. 1997. Increased cholecystokinin and pancreatic polypeptide responses to a fat-rich meal in patients with restrictive but not bulimic anorexia nervosa. Biol Psychiatry. 41(10):1068–1070. https://doi.org/10.1016/S0006-3223(97)00044-9

Fujita N et al. 1999. Methylation-mediated transcriptional silencing in euchromatin by methyl-CpG binding protein MBD1 isoforms. Mol Cell Biol. 19(9):6415–6426. https://doi.org/10.1128/MCB.19.9.6415

Fukushima M et al. 1993. Insulin sensitivity, insulin secretion, and glucose effectiveness in anorexia nervosa: a minimal model analysis. Metabolism. 42(9):1164–1168. https://doi.org/10.1016/0026-0495(93)90275-s

Furuta S et al. 1999. Anorexia nervosa with severe liver dysfunction and subsequent critical complications. Intern Med. 38(7):575–579. https://doi.org/10.2169/internalmedicine.38.575

Gabriel FC, Fantuzzi G. 2019. The association of short-chain fatty acids and leptin metabolism: a systematic review. Nutr Res. 72:18–35. https://doi.org/10.1016/j.nutres.2019.08.006

Gale CR et al. 2016. Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank. Transl Psychiatry. 6(4):e791–e791. https://doi.org/10.1038/tp.2016.56.

Gallagher D, Parker A, Samavat H, Zelig R. 2022. Prophylactic supplementation of phosphate, magnesium, and potassium for the prevention of refeeding syndrome in hospitalized individuals with anorexia nervosa. Nutr Clin Pract. 37(2):328–343. https://doi.org/10.1002/ncp.10786

Galusca B et al. 2015. Neuropeptide Y and α-MSH circadian levels in two populations with low body weight: anorexia nervosa and constitutional thinness. PLoS One. 10(3):e0122040. https://doi.org/10.1371/journal.pone.0122040

Garber AK et al. 2019. Weight loss and illness severity in adolescents with atypical anorexia nervosa. Pediatrics. 144(6) https://doi.org/10.1542/peds.2019-2339

Garcia N, Gutierrez E. 2023. Anorexia nervosa and microbiota: systematic review and critical appraisal. Eat Weight Disord. 28(1):1. https://doi.org/10.1007/s40519-023-01529-4

Gatti D et al. 2015. Strong relationship between vitamin D status and bone mineral density in anorexia nervosa. Bone. 78:212–215. https://doi.org/10.1016/j.bone.2015.05.014

Gaudio S, Carducci F, Piervincenzi C, Olivo G, Schiöth HB. 2019. Altered thalamo–cortical and occipital–parietal–temporal–frontal white matter connections in patients with anorexia and bulimia nervosa: a systematic review of diffusion tensor imaging studies. J Psychiatry Neurosci. 44(5):324–339. https://doi.org/10.1503/jpn.180121

Gaudio S, Wiemerslage L, Brooks SJ, Schiöth HB. 2016. A systematic review of resting-state functional-MRI studies in anorexia nervosa: evidence for functional connectivity impairment in cognitive control and visuospatial and body-signal integration. Neurosci Biobehav Rev. 71:578–589. https://doi.org/10.1016/j.neubiorev.2016.09.032

Ge X et al. 2018. LEAP2 is an endogenous antagonist of the ghrelin receptor. Cell Metab. 27(2):461–469.e6. e466. https://doi.org/10.1016/j.cmet.2017.10.016

Geer B et al. 2019. Metformin abuse: a novel and dangerous purging behavior in anorexia nervosa. Int J Eat Disord. 52(3):319–321. https://doi.org/10.1002/eat.23010.

Geisler D et al. 2020. Altered global brain network topology as a trait marker in patients with anorexia nervosa. Psychol Med. 50(1):107–115. https://doi.org/10.1017/S0033291718004002

Geisler D et al. 2016. Abnormal functional global and local brain connectivity in female patients with anorexia nervosa. J Psychiatry Neurosci. 41(1):6–15. https://doi.org/10.1503/jpn.140310

Geisler D et al. 2022. Altered white matter connectivity in young acutely underweight patients with anorexia

nervosa. J Am Acad Child Adolesc Psychiatry. 61(2):331–340. https://doi.org/10.1016/j.jaac.2021.04.019
Geracioti TD, Liddle RA, Altemus M, Demitrack MA, Gold PW. 1992. Regulation of appetite and cholecystokinin secretion in anorexia nervosa. Am J Psychiatry. 149(7):958–961., P. https://doi.org/10.1176/ajp.149.7.958
Gerlach M et al. 2016. Therapeutic drug monitoring as a measure of proactive pharmacovigilance in child and adolescent psychiatry. Expert Opin Drug Saf. 15(11):1477–1482. https://doi.org/10.1080/14740338.2016.1225721
Germain N et al. 2007. Constitutional thinness and lean anorexia nervosa display opposite concentrations of peptide YY, glucagon-like peptide 1, ghrelin, and leptin. Am J Clin Nutr. 85(4):967–971. https://doi.org/10.1093/ajcn/85.4.967
Germain N et al. 2023. Continuous glucose monitoring assessment in patients suffering from anorexia nervosa reveals chronic prolonged mild hypoglycemia all over the nycthemeron. Eur Eat Disord Rev. 31(3):402–412. https://doi.org/10.1002/erv.2963
Gherbesi E et al. 2024. Myocardial mechanics in anorexia nervosa: a systematic review and meta-analysis of speckle tracking echocardiographic studies. J Cardiovasc Med (Hagerstown). 25(10):740–748. https://doi.org/10.2459/jcm.0000000000001661
Gibson D, Mehler PS. 2019. Anorexia nervosa and the immune system-a narrative review. J Clin Med. 8(11):1915. https://doi.org/10.3390/jcm8111915
Gibson D, Mehler PS. 2024. A new conceptual model for anorexia nervosa: a role for connective tissue? Int J Eat Disord. 57(3):537–542. https://doi.org/10.1002/eat.24172.
Gibson D et al. 2024. Associations between low body weight, weight loss, and medical instability in adults with eating disorders. Int J Eat Disord. 57(4):869–878. https://doi.org/10.1002/eat.24129.
Gibson D, Watters A, Bauschka M. 2023. Seizures in eating disorders. Int J Eat Disord. 56(8):1650–1660. https://doi.org/10.1002/eat.23969
Gibson D, Watters A, Cost J, Mascolo M, Mehler PS. 2020. Extreme anorexia nervosa: medical findings, outcomes, and inferences from a retrospective cohort. J Eat Disord. 8(1):25. https://doi.org/10.1186/s40337-020-00303-6
Giel K, Zipfel S, Hallschmid M. 2018. Oxytocin and eating disorders: a narrative review on emerging findings and perspectives. Curr Neuropharmacol. 16(8):1111–1121. https://doi.org/10.2174/1570159X15666171128143158
Giollo A et al. 2017. Vitamin D levels strongly influence bone mineral density and bone turnover markers during weight gain in female patients with anorexia nervosa. Int J Eat Disord. 50(9):1041–1049. https://doi.org/10.1002/eat.22731
Glenny EM et al. 2021. Gut microbial communities from patients with anorexia nervosa do not influence body weight in recipient germ-free mice. Gut Microbes. 13(1):1–15. https://doi.org/10.1080/19490976.2021.1897216
Gold PW et al. 1986. Abnormal hypothalamic-pituitary-adrenal function in anorexia nervosa. Pathophysiologic mechanisms in underweight and weight-corrected patients. N Engl J Med. 314(21):1335–1342. &. https://doi.org/10.1056/nejm198605223142102
Golden NH, Walsh BT. 2024. Time to revisit the definition of atypical anorexia nervosa. Int J Eat Disord. 57(4):757–760. https://doi.org/10.1002/eat.24174
Goldschmidt AB et al. 2018. Ecological momentary assessment of maladaptive eating in children and adolescents with overweight or obesity. Int J Eat Disord. 51(6):549–557. https://doi.org/10.1002/eat.22864.
Gonzalez-Ortiz F et al. 2023a. Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. Mol Neurodegener. 18(1):18. https://doi.org/10.1186/s13024-023-00605-8
Gonzalez-Ortiz F et al. 2023b. Brain-derived tau: a novel blood-based biomarker for Alzheimer's disease-type neurodegeneration. Brain. 146(3):1152–1165. https://doi.org/10.1093/brain/awac407
Gorwood P et al. 2016. New insights in anorexia nervosa. Front Neurosci. 10:256. https://doi.org/10.3389/fnins.2016.00256
Gradl-Dietsch G et al. 2023. Rapid emergence of appetite and hunger resulting in weight gain and improvement of eating disorder symptomatology during and after short-term off-label metreleptin treatment of a patient with anorexia nervosa. Obes Facts. 16(1):99–107. https://doi.org/10.1159/000527386
Grigioni S et al. 2022. Intestinal permeability and appetite regulating peptides-reactive immunoglobulins in severely malnourished women with anorexia nervosa. Clin Nutr. 41(8):1752–1758. https://doi.org/10.1016/j.clnu.2022.06.036.
Grosser J et al. 2020. Psychological and nutritional correlates of objectively assessed physical activity in patients with anorexia nervosa. Eur Eat Disord Rev. 28(5):559–570. https://doi.org/10.1002/erv.2756
Grzelak T et al. 2018a. Neuropeptide B and vaspin as new biomarkers in anorexia nervosa. Biomed Res Int. 2018(1):9727509–9727508. https://doi.org/10.1155/2018/9727509
Grzelak T et al. 2018b. Vaspin (but not neuropeptide B or neuropeptide W) as a possible predictor of body weight normalization in anorexia nervosa. Arch Med Sci. 17(2):376–381. https://doi.org/10.5114/aoms.2018.74969
Guarasci F et al. 2018. Aging and nutrition induce tissue-specific changes on global DNA methylation status in rats. Mech Ageing Dev. 174:47–54. https://doi.org/10.1016/j.mad.2018.02.001
Guerdjikova AI, Ward A, Ontiveros M, McElroy SL. 2024. Semaglutide misuse in atypical anorexia nervosa-a case report. J Clin Psychopharmacol. 44(2):179–180. https://doi.org/10.1097/jcp.0000000000001820
Gull WW. 1997. Anorexia nervosa (apepsia hysterica, anorexia hysterica). 1868. Obes Res. 5(5):498–502. https://doi.org/10.1002/j.1550-8528.1997.tb00677.x
Gurevich E, Steiling S, Landau D. 2021. Incidence of impaired kidney function among adolescent patients hospitalized with anorexia nervosa. JAMA Netw Open. 4(11):e2134908. https://doi.org/10.1001/jamanetworkopen.2021.34908
Gutierrez E, García N, Carrera O. 2024. Disordered eating in anorexia nervosa: give me heat, not just food. Front Public Health. 12:1433470. https://doi.org/10.3389/fpubh.2024.1433470
Habib KE, Gold PW, Chrousos GP. 2001. Neuroendocrinology of stress. Endocrinol Metab Clin North Am. 30(3):695–728. https://doi.org/10.1016/s0889-8529(05)70208-5
Hadigan CM et al. 2000. Assessment of macronutrient and micronutrient intake in women with anorexia nervosa. Int J Eat Disord. 28(3):284–292. https://doi.org/10.1002/1098-108X(200011)28:3<284::AID-EAT5>3.0.CO;2-G
Hagemann CA et al. 2022. LEAP2 reduces postprandial glucose excursions and ad libitum food intake in healthy men. Cell Rep Med. 3(4):100582. https://doi.org/10.1016/j.xcrm.2022.100582

Haines MS. 2023. Endocrine complications of anorexia nervosa. J Eat Disord. 11(1):24. https://doi.org/10.1186/s40337-023-00744-9
Halbeisen G, Amin L, Braks K, Huber TJ, Paslakis G. 2024. Acute activity urges predict lower early weight gain during inpatient treatment for anorexia nervosa. Int J Eat Disord. 57(12):2452–2460. https://doi.org/10.1002/eat.24305
Hanachi M et al. 2019. Micronutrients deficiencies in 374 severely malnourished anorexia nervosa inpatients. Nutrients. 11(4):792. https://doi.org/10.3390/nu11040792
Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. 2019. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. 11(1):34. https://doi.org/10.1186/s13195-019-0485-0
Harari GM et al. 2016. Using smartphones to collect behavioral data in psychological science: opportunities, practical considerations, and challenges. Perspect Psychol Sci. 11(6):838–854. https://doi.org/10.1177/1745691616650285.
Hasselbalch KC, Lanng KR, Birkeland M, Sjögren M. 2020. Potential shortcomings in current studies on the effect of intranasal oxytocin in Anorexia Nervosa and healthy controls-a systematic review and meta-analysis. Psychopharmacology (Berl). 237(10):2891–2903. https://doi.org/10.1007/s00213-020-05626-5
Hata T et al. 2019. The gut microbiome derived from anorexia nervosa patients impairs weight gain and behavioral performance in female mice. Endocrinology. 160(10):2441–2452. https://doi.org/10.1210/en.2019-00408
Hay P et al. 2023. Epidemiology of eating disorders: population, prevalence, disease burden and quality of life informing public policy in Australia-a rapid review. J Eat Disord. 11(1):23. https://doi.org/10.1186/s40337-023-00738-7.
Hebebrand J et al. 2003. Hyperactivity in patients with anorexia nervosa and in semistarved rats: evidence for a pivotal role of hypoleptinemia. Physiol Behav. 79(1):25–37. https://doi.org/10.1016/s0031-9384(03.)00102-1
Hebebrand J et al. 2022. The role of hypoleptinemia in the psychological and behavioral adaptation to starvation: implications for anorexia nervosa. Neurosci Biobehav Rev. 141:104807. https://doi.org/10.1016/j.neubiorev.2022.104807
Hebebrand J, Hinney A, Antel J. 2023. Could leptin substitution therapy potentially terminate entrapment in anorexia nervosa? Nat Rev Endocrinol. 19(8):435–436. https://doi.org/10.1038/s41574-023-00863-y.
Hebebrand J et al. 2019. Clinical trials required to assess potential benefits and side effects of treatment of patients with anorexia nervosa with recombinant human leptin. Front Psychol. 10:769. https://doi.org/10.3389/fpsyg.2019.00769.
Hebebrand J et al. 2024. Does hypoleptinemia trigger entrapment in anorexia nervosa? Etiological and clinical considerations. Eur Eat Disord Rev. 32(3):557–574. https://doi.org/10.1002/erv.3071
Hebebrand J et al. 2024. Premorbid body weight predicts weight loss in both anorexia nervosa and atypical anorexia nervosa: further support for a single underlying disorder. Int J Eat Disord. 57(4):967–982. https://doi.org/10.1002/eat.24189
Hebebrand J, Seitz J, Matthews A. 2025. Considering sufficient weight loss as a prerequisite for development of anorexia nervosa and atypical anorexia nervosa. Int J Eat Disord. 58(1):162–167. https://doi.org/10.1002/eat.24313.
Hebebrand J et al. 2022. First account of psychological changes perceived by a female with congenital leptin deficiency upon treatment with metreleptin. Obes Facts. 15(5):730–735. https://doi.org/10.1159/000526169
Hedman A et al. 2019. Bidirectional relationship between eating disorders and autoimmune diseases. J Child Psychol Psychiatry. 60(7):803–812. https://doi.org/10.1111/jcpp.12958
Heinz MV et al. 2024. Evaluating therabot: a randomized control trial investigating the feasibility and effectiveness of a generative AI therapy Chatbot for depression, anxiety, and eating disorder symptom treatment, anxiety, and eating disorder symptom treatment. OSF Preprint. https://doi.org/10.31234/osf.io/pjqmr
Hellerhoff I et al. 2023. Serum neurofilament light concentrations are associated with cortical thinning in anorexia nervosa. Psychol Med. 53(15):7053–7061. https://doi.org/10.1017/S0033291723000387
Hellerhoff I et al. 2021. Differential longitudinal changes of neuronal and glial damage markers in anorexia nervosa after partial weight restoration. Transl Psychiatry. 11(1):86. https://doi.org/10.1038/s41398-021-01209-w
Herle M et al. 2021. The genomics of childhood eating behaviours. Nat Hum Behav. 5(5):625–630. https://doi.org/10.1038/s41562-020-01019-y
Heruc GA et al. 2018a. Appetite perceptions, gastrointestinal symptoms, ghrelin, peptide YY and state anxiety are disturbed in adolescent females with anorexia nervosa and only partially restored with short-term refeeding. Nutrients. 11(1):59. https://doi.org/10.3390/nu11010059.
Heruc GA et al. 2018b. Effects of starvation and short-term refeeding on gastric emptying and postprandial blood glucose regulation in adolescent girls with anorexia nervosa. Am J Physiol Endocrinol Metab. 315(4):E565–e573. https://doi.org/10.1152/ajpendo.00149.2018.
Het S et al. 2015. Blunted neuroendocrine stress reactivity in young women with eating disorders. J Psychosom Res. 78(3):260–267. https://doi.org/10.1016/j.jpsychores.2014.11.001.
Hiemke C et al. 2018. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 51(1-02):9–62. https://doi.org/10.1055/s-0043-116492
Hillebrand JJ, Kas MJ, Adan RA. 2005. a-MSH enhances activity-based anorexia. Peptides. 26(10):1690–1696. https://doi.org/10.1016/j.peptides.2004.11.027
Himmerich H, Keeler JL, Tchanturia K, Treasure J. 2024. Treatment escalation for people with anorexia nervosa: setting, therapies and nutritional interventions. Curr Opin Psychiatry. 37(6):404–416. https://doi.org/10.1097/yco.0000000000000964
Himmerich H, Patsalos O, Lichtblau N, Ibrahim MA, Dalton B. 2019. Cytokine research in depression: principles, challenges, and open questions. Front Psychiatry. 10:30. https://doi.org/10.3389/fpsyt.2019.00030
Himmerich H, Schönknecht P, Heitmann S, Sheldrick AJ. 2010. Laboratory parameters and appetite regulators in patients with anorexia nervosa. J Psychiatr Pract. 16(2):82–92. https://doi.org/10.1097/01.pra.0000369969.87779.1c
Himmerich H, Treasure J. 2024. Anorexia nervosa: diagnostic, therapeutic, and risk biomarkers in clinical practice. Trends Mol Med. 30(4):350–360. https://doi.org/10.1016/j.molmed.2024.01.002
Hirtz R, Hinney A. 2020. Genetic and epigenetic findings in anorexia nervosa. Medizinische Genetik. 32(1):25–29. https://doi.org/10.1515/medgen-2020-2005

Hofmann T et al. 2014. Irisin levels are not affected by physical activity in patients with anorexia nervosa. Front Endocrinol (Lausanne). 4:202. https://doi.org/10.3389/fendo.2013.00202

Holtkamp K et al. 2006. Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. Biol Psychiatry. 60(3):311–313. https://doi.org/10.1016/j.biopsych.2005.11.001

Horie K et al. 2023. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. Nat Med. 29(8):1954–1963. https://doi.org/10.1038/s41591-023-02443-z

Hübel C et al. 2021. One size does not fit all. Genomics differentiates among anorexia nervosa, bulimia nervosa, and binge-eating disorder. Int J Eat Disord. 54(5):785–793. https://doi.org/10.1002/eat.23481

Hübel C et al. 2019. Genomics of body fat percentage may contribute to sex bias in anorexia nervosa. Am J Med Genet B Neuropsychiatr Genet. 180(6):428–438. / https://doi.org/10.1002/ajmg.b.32709.

Hübel C, Marzi SJ, Breen G, Bulik CM. 2019. Epigenetics in eating disorders: a systematic review. Mol Psychiatry. 24(6):901–915. https://doi.org/10.1038/s41380-018-0254-7

Hübel C et al. 2019. Body composition in anorexia nervosa: meta-analysis and meta-regression of cross-sectional and longitudinal studies. Int J Eat Disord. 52(11):1205–1223. https://doi.org/10.1002/eat.23158

Huckins JF et al. 2019. Fusing mobile phone sensing and brain imaging to assess depression in college students. Front Neurosci. 13:248. https://doi.org/10.3389/fnins.2019.00248

Huckins LM. 2023. Thoughtful phenotype definitions empower participants and power studies. Complex Psychiatry. 8(3–4):57–62. https://doi.org/10.1159/000527022

Huckins LM et al. 2018. Investigation of common, low-frequency and rare genome-wide variation in anorexia nervosa. Mol Psychiatry. 23(5):1169–1180. https://doi.org/10.1038/mp.2017.88

Hucklebridge F, Clow A, Evans P. 1998. The relationship between salivary secretory immunoglobin A and cortisol: neuroendocrine response to awakening and the diurnal cycle. Int J Psychophysiol. 31(1):69–76. https://doi.org/10.1016/s0167-8760(98)00042-7

Hussain AA et al. 2024. A naturalistic study of plasma lipid alterations in female patients with anorexia nervosa before and after weight restoration treatment. J Eat Disord. 12(1):92. https://doi.org/10.1186/s40337-024-01055-3

Hussain AA et al. 2019. Increased lipid and lipoprotein concentrations in anorexia nervosa: a systematic review and meta-analysis. Int J Eat Disord. 52(6):611–629. https://doi.org/10.1002/eat.23051

Hütter G, Ganepola S, Hofmann WK. 2009. The hematology of anorexia nervosa. Int J Eat Disord. 42(4):293–300. https://doi.org/10.1002/eat.20610

Inamdar NM, Ehrlich KC, Ehrlich M. 1991. CpG methylation inhibits binding of several sequence-specific DNA-binding proteins from pea, wheat, soybean and cauliflower. Plant Mol Biol. 17(1):111–123. https://doi.org/10.1007/BF00036811

Insel TR. 2017. Digital phenotyping: technology for a new science of behavior. JAMA. 318(13):1215–1216. https://doi.org/10.1001/jama.2017.11295

Iranzo-Tatay C et al. 2022. Genome-wide DNA methylation profiling in anorexia nervosa discordant identical twins. Transl Psychiatry. 12(1):15. https://doi.org/10.1038/s41398-021-01776-y

Jada K et al. 2021. The pathophysiology of Anorexia Nervosa in hypothalamic endocrine function and bone metabolism. Cureus. 13(12):e20548. https://doi.org/10.7759/cureus.20548

Jagielska G et al. 2013. Assessment of neuropeptide Y, leptin and leptin-receptor concentrations in teenagers suffering from anorexia nervosa. Ginekol Pol. 84(4):268–276.

Jagielska G et al. 2017. Bone mineralization and densitometric evaluation of vertebral fractures in women 6-21 years after the onset of anorexia nervosa symptoms. Psychiatr Pol. 51(2):231–246. https://doi.org/10.12740/pp/63149 (Original work published Mineralizacja kości i ocena densytometryczna złamań kręgosłupa u kobiet po upływie 6–21 lat od pojawienia się objawów jadłowstrętu psychicznego.)

Janzen ML et al. 2020. Changes to the electrocardiogram during exercise in anorexia nervosa. J Electrocardiol. 61:99–105. https://doi.org/10.1016/j.jelectrocard.2020.06.012

Javelot H, Messaoudi M, Garnier S, Rougeot C. 2010. Human opiorphin is a naturally occurring antidepressant acting selectively on enkephalin-dependent delta-opioid pathways. J Physiol Pharmacol. 61(3):355–362. https://doi.org/10.1073/pnas.0605865103

Jenkins ZM et al. 2022. Autonomic nervous system function in women with anorexia nervosa. Clin Auton Res. 32(1):29–42. https://doi.org/10.1007/s10286-021-00836-z

Ji W et al. 2024. Mendelian randomization studies of risk and protective factors for osteoporosis: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 15:1486188. https://doi.org/10.3389/fendo.2024.1486188

Jia Y et al. 2023. Association between human blood metabolome and the risk of psychiatric disorders. Schizophr Bull. 49(2):428–443. https://doi.org/10.1093/schbul/sbac130

Jiang L, Zuo X-N. 2016. Regional homogeneity: a multimodal, multiscale neuroimaging marker of the human connectome. Neuroscientist. 22(5):486–505. https://doi.org/10.1177/1073858415595004

Jomah S et al. 2024. Cardiac involvement and its clinical significance in patients with anorexia nervosa. Eur J Pediatr. 183(1):95–102. https://doi.org/10.1007/s00431-023-05305-5

Juarascio AS, Manasse SM, Goldstein SP, Forman EM, Butryn ML. 2015. Review of smartphone applications for the treatment of eating disorders. Eur Eat Disord Rev. 23(1):1–11. https://doi.org/10.1002/erv.2327

Justine P et al. 2022. Left ventricular strains and myocardial work in adolescents with anorexia nervosa. Front Cardiovasc Med. 9:798774. https://doi.org/10.3389/fcvm.2022.798774

Kanbur NO et al. 2009. Second-degree atrioventricular block (Mobitz Type I) in an adolescent with anorexia nervosa: intrinsic or acquired conduction abnormality. Int J Eat Disord. 42(6):575–578. https://doi.org/10.1002/eat.20647

Kappou K et al. 2021. Neuroimaging findings in adolescents and young adults with anorexia nervosa: a systematic review. Children (Basel). 8(2):137. https://doi.org/10.3390/children8020137

Karageorgiou V et al. 2020. Adipokines in anorexia nervosa: a systematic review and meta-analysis. Psychoneuroendocrinology. 112:104485. https://doi.org/10.1016/j.psyneuen.2019.104485

Karavia A et al. 2024. Using electroencephalogram-extracted nonlinear complexity and wavelet-extracted power rhythm features during the performance of demanding cognitive tasks (Aristotle's Syllogisms) in optimally classifying

patients with anorexia nervosa. Brain Sci. 14(3):251. https://doi.org/10.3390/brainsci14030251

Karr TM et al. 2017. Examining physical activity and affect using objective measures: a pilot study of anorexia nervosa. Sport J. 20. https://thesportjournal.org/article/examining-physical-activity-and-affectusing-objective-measures-a-pilot-study-of-anorexia-nervosa/

Karwautz A et al. 2024. Therapeutic drug monitoring in adolescents with anorexia nervosa for safe treatment with adjunct olanzapine. Eur Eat Disord Rev. 32(6):1055–1068. https://doi.org/10.1002/erv.3022

Kaufmann L-K et al. 2017. Fornix under water? Ventricular enlargement biases forniceal diffusion magnetic resonance imaging indices in anorexia nervosa. Biol Psychiatry Cogn Neurosci Neuroimaging. 2(5):430–437. https://doi.org/10.1016/j.bpsc.2017.03.014

Kaufmann L-K et al. 2020. Age influences structural brain restoration during weight gain therapy in anorexia nervosa. Transl Psychiatry. 10(1):126. https://doi.org/10.1038/s41398-020-0809-7

Kaufmann L-K et al. 2023. Disrupted longitudinal restoration of brain connectivity during weight normalization in severe anorexia nervosa. Transl Psychiatry. 13(1):136. https://doi.org/10.1038/s41398-023-02428-z

Käver L et al. 2024. Epigenetic alterations in patients with anorexia nervosa—a systematic review. Mol Psychiatry. 29(12):3900–3914. https://doi.org/10.1038/s41380-024-02601-w

Kaye WH, Berrettini W, Gwirtsman H, George DT. 1990. Altered cerebrospinal fluid neuropeptide Y and peptide YY immunoreactivity in anorexia and bulimia nervosa. Arch Gen Psychiatry. 47(6):548–556. https://doi.org/10.1001/archpsyc.1990.01810180048008

Kaye WH et al. 1987. Elevated cerebrospinal fluid levels of immunoreactive corticotropin-releasing hormone in anorexia nervosa: relation to state of nutrition, adrenal function, and intensity of depression. J Clin Endocrinol Metab. 64(2):203–208. https://doi.org/10.1210/jcem-64-2-203

Keeler JL et al. 2024. Longitudinal changes in brain-derived neurotrophic factor (BDNF) but not cytokines contribute to hippocampal recovery in anorexia nervosa above increases in body mass index. Psychol Med. 54(9):2242–2253. https://doi.org/10.1017/S0033291724000394

Keeler, J. L., Bovenberg, C., Himmerich, H., Treasure, J., Carter, B., Schmidt, U., & Dalton, B. (Accepted.). A comprehensive updated cross-sectional and longitudinal meta-analysis of cytokines in eating disorders.

Keeler JL, Kan C, Treasure J, Himmerich H. 2024. Novel treatments for anorexia nervosa: insights from neuroplasticity research. Euro Eating Disorders Rev. 32(6):1069–1084. https://doi.org/10.1002/erv.3039

Keeler JL et al. 2022a. Serum levels of brain-derived neurotrophic factor and association with pro-inflammatory cytokines in acute and recovered anorexia nervosa. J Psychiatr Res. 150:34–39. https://doi.org/10.1016/j.jpsychires.2022.03.031

Keeler JL et al. 2022b. Difficulties in retrieving specific details of autobiographical memories and imagining positive future events in individuals with acute but not remitted anorexia nervosa. J Eat Disord. 10(1):172. https://doi.org/10.1186/s40337-022-00684-w

Keeler JL et al. 2022c. Growth factors in anorexia nervosa: a systematic review and meta-analysis of cross-sectional and longitudinal data. World J Biol Psychiatry. 23(8):582–600. https://doi.org/10.1080/15622975.2021.2015432

Keeler JL, Treasure J, Juruena MF, Kan C, Himmerich H. 2021. Ketamine as a treatment for anorexia nervosa: a narrative review. Nutrients. 13(11):4158. https://doi.org/10.3390/nu13114158

Keeler JL et al. 2025. A systematic review and meta-analysis of routine white blood cell concentrations in people with eating disorders. Neuroscience. https://doi.org/10.1016/j.neuroscience.2025.12.045

Keizer A, van Elburg A, Helms R, Dijkerman HC. 2016. A virtual reality full body illusion improves body image disturbance in anorexia nervosa. PLoS One. 11(10):e0163921. https://doi.org/10.1371/journal.pone.0163921

Kershaw EE, Flier JS. 2004. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 89(6):2548–2556. https://doi.org/10.1210/jc.2004-0395

Keshen A et al. 2020. Efficacy and acceptability of self-monitoring via a smartphone application versus traditional paper records in an intensive outpatient eating disorder treatment setting. Eur Eat Disord Rev. 28(4):473–479. https://doi.org/10.1002/erv.2727.

Kesselmeier M et al. 2018. High-throughput DNA methylation analysis in anorexia nervosa confirms TNXB hypermethylation. World J Biol Psychiatry. 19(3):187–199. https://doi.org/10.1080/15622975.2016.1190033

Ketel J et al. 2024. Gastrointestinal microbiota & symptoms of depression and anxiety in anorexia nervosa-a re-analysis of the MICROBIAN longitudinal study. Nutrients. 16(6):891. https://doi.org/10.3390/nu16060891.

Keys A, Brožek J, Henschel A, Mickelsen O, Taylor HL. 1950. The biology of human starvation. 2 Vols. University of Minnesota Press.

Khairova RA, Machado-Vieira R, Du J, Manji HK. 2009. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychopharmacol. 12(4):561–578. https://doi.org/10.1017/S1461145709009924

Khalil M et al. 2024. Neurofilaments as biomarkers in neurological disorders - towards clinical application. Nat Rev Neurol. 20(5):269–287. https://doi.org/10.1038/s41582-024-00955-x

Khan MU, Patel AG, Wilbur SL, Khan IA. 2007. Electrocardiographic changes in combined electrolyte depletion. Int J Cardiol. 116(2):276–278. https://doi.org/10.1016/j.ijcard.2006.04.070.

Khatri V, Bauschka M, Foley M, Lundberg C, Mehler P. 2023. A multi-disciplinary approach to managing end-stage renal disease in anorexia nervosa: a case report. Clin Med Insights Case Rep. 16:11795476231169385. https://doi.org/10.1177/11795476231169385

Kheloufi M, Boulanger CM, Durand F, Rautou PE. 2014. Liver autophagy in anorexia nervosa and acute liver injury. Biomed Res Int. 2014:701064–701010. https://doi.org/10.1155/2014/701064

Kilshaw RE et al. 2022. Passive sensor data for characterizing states of increased risk for eating disorder behaviors in the digital phenotyping arm of the binge eating genetics initiative: protocol for an observational study. JMIR Res Protoc. 11(6):e38294. https://doi.org/10.2196/38294

Kimball A et al. 2022. Dehydroepiandrosterone sulfate levels predict weight gain in women with anorexia nervosa. Int J Eat Disord. 55(8):1100–1107. https://doi.org/10.1002/eat.23767

Kimura A, Namekata K, Guo X, Harada C, Harada T. 2016. Neuroprotection, growth factors and BDNF-TrkB signalling in retinal degeneration. Int J Mol Sci. 17(9):1584. https://doi.org/10.3390/ijms17091584

King JA, Frank GK, Thompson PM, Ehrlich S. 2018. Structural neuroimaging of anorexia nervosa: future directions in the quest for mechanisms underlying dynamic alterations. Biol Psychiatry. 83(3):224–234. https://doi.org/10.1016/j.biopsych.2017.08.011

Kirichenko TV et al. 2022. The role of adipokines in inflammatory mechanisms of obesity. Int J Mol Sci. 23(23):14982. https://doi.org/10.3390/ijms232314982

Kirkham TC, Williams CM, Fezza F, Di Marzo V. 2002. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. Br J Pharmacol. 136(4):550–557. https://doi.org/10.1038/sj.bjp.0704767

Kirschbaum C, Hellhammer DH. 1989. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology. 22(3):150–169. https://doi.org/10.1159/000118611

Kleiman SC et al. 2015. The intestinal microbiota in acute anorexia nervosa and during renourishment: relationship to depression, anxiety, and eating disorder psychopathology. Psychosom Med. 77(9):969–981. https://doi.org/10.1097/psy.0000000000000247.

Klein AB et al. 2011. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J Neuropsychopharmacol. 14(3):347–353. https://doi.org/10.1017/S1461145710000738

Klump KL. 2013. Puberty as a critical risk period for eating disorders: a review of human and animal studies. Horm Behav. 64(2):399–410. https://doi.org/10.1016/j.yhbeh.2013.02.019

Klump KL, Burt SA, McGue M, Iacono WG. 2007. Changes in genetic and environmental influences on disordered eating across adolescence: a longitudinal twin study. Arch Gen Psychiatry. 64(12):1409–1415. https://doi.org/10.1001/archpsyc.64.12.1409

Klump KL et al. 2012. The effects of puberty on genetic risk for disordered eating: evidence for a sex difference. Psychol Med. 42(3):627–637. https://doi.org/10.1017/S0033291711001541.

Kohn MR, Golden NH, Shenker IR. 1998. Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa. J Adolesc Health. 22(3):239–243. https://doi.org/10.1016/s1054-139x(97)00163-8

Koklesova L et al. 2021. Homocysteine metabolism as the target for predictive medical approach, disease prevention, prognosis, and treatments tailored to the person. Epma J. 12(4):477–505. https://doi.org/10.1007/s13167-021-00263-0

Kolar DR, Hammerle F, Jenetzky E, Huss M, Bürger A. 2016. Aversive tension in female adolescents with Anorexia Nervosa: a controlled ecological momentary assessment using smartphones. BMC Psychiatry. 16(1):97. https://doi.org/10.1186/s12888-016-0807-8.

Koomar T, Thomas TR, Pottschmidt NR, Lutter M, Michaelson JJ. 2021. Estimating the prevalence and genetic risk mechanisms of ARFID in a large autism cohort. Front Psychiatry. 12:668297. https://doi.org/10.3389/fpsyt.2021.668297

Koschke M et al. 2010. Increased QT variability in patients with anorexia nervosa--an indicator for increased cardiac mortality? Int J Eat Disord. 43(8):743–750. https://doi.org/10.1002/eat.20765

Koshimizu H, Hazama S, Hara T, Ogura A, Kojima M. 2010. Distinct signaling pathways of precursor BDNF and mature BDNF in cultured cerebellar granule neurons. Neurosci Lett. 473(3):229–232. https://doi.org/10.1016/j.neulet.2010.02.055

Kowiański P et al. 2018. BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity. Cell Mol Neurobiol. 38(3):579–593. https://doi.org/10.1007/s10571-017-0510-4

Koyama KI et al. 2010. Changes in acyl ghrelin, des-acyl ghrelin, and ratio of acyl ghrelin to total ghrelin with short-term refeeding in female inpatients with restricting-type anorexia nervosa. Horm Metab Res. 42(8):595–598. https://doi.org/10.1055/s-0030-1252017

Kramer A et al. 2025. Towards recommendations for cost-effectiveness analysis of predictive, prognostic, and serial biomarker tests in oncology. Pharmacoeconomics. 43(5):483–497. https://doi.org/10.1007/s40273-025-01470-7

Krantz MJ et al. 2020. Is QTc-interval prolongation an inherent feature of eating disorders? A cohort study. Am J Med. 133(9):1088–1094.e1. e1081. https://doi.org/10.1016/j.amjmed.2020.02.015

Krantz MJ, Mehler PS. 2004. Resting tachycardia, a warning sign in anorexia nervosa: case report. BMC Cardiovasc Disord. 4(1):10. https://doi.org/10.1186/1471-2261-4-10

Krauss H et al. (2025). Efficacy of adjunct Olanzapine treatment in adolescents with Anorexia Nervosa: a comparison of two patient cohorts. Eur Eat Disord Rev. 33(6):1314–1320. https://doi.org/10.1002/erv.70009

Kumar S, Mankowski RT, Anton SD, Babu Balagopal P. 2021. Novel insights on the role of spexin as a biomarker of obesity and related cardiometabolic disease. Int J Obes (Lond). 45(10):2169–2178. https://doi.org/10.1038/s41366-021-00906-2

Kuwabara M, Niwa K, Yamada U, Ohta D. 2018. Low body mass index correlates with low left ventricular mass index in patients with severe anorexia nervosa. Heart Vessels. 33(1):89–93. https://doi.org/10.1007/s00380-017-1051-y

La Sala MS et al. 2013. Modulation of taste responsiveness by the satiation hormone peptide YY. Faseb J. 27(12):5022–5033. https://doi.org/10.1096/fj.13-228064

Lacroix A, Feelders RA, Stratakis CA, Nieman LK. 2015. Cushing's syndrome. Lancet. 386(9996):913–927. https://doi.org/10.1016/s0140-6736(14)61375-1

Lai CW, Jiang HJ, Hsiao PJ. 2017. Manifestation of hyperaldosteronism related hypokalemia in a case of anorexia nervosa. Kaohsiung J Med Sci. 33(10):533–534. https://doi.org/10.1016/j.kjms.2017.06.004

Lamzabi I et al. 2015. Myocardial changes in a patient with anorexia nervosa: a case report and review of literature. Am J Clin Pathol. 143(5):734–737. https://doi.org/10.1309/ajcp4plff1ttkent

Langlet B et al. 2021. Physical activity and sleep during the first week of anorexia nervosa inpatient care. PLoS One. 16(11):e0260077. https://doi.org/10.1371/journal.pone.0260077

Larsen JT et al. 2021. Anorexia nervosa and inflammatory bowel diseases-Diagnostic and genetic associations. JCPP Adv. 1(4):e12036. https://doi.org/10.1002/jcv2.12036

Lawson EA et al. 2011. Appetite-regulating hormones cortisol and peptide YY are associated with disordered eating psychopathology, independent of body mass index. Eur J Endocrinol. 164(2):253–261. https://doi.org/10.1530/eje-10-0523

Lawson EA et al. 2012. Plasma sodium level is associated with bone loss severity in women with anorexia nervosa. J Clin Psychiatry. 73(11):e1379–e1383. https://doi.org/10.4088/JCP.12m07919

Leach K, Bauschka M, Watters A, Mehler PS. 2024. Medical and psychiatric characteristics of patients hospitalized for severe restrictive eating disorders: analysis of 545 consecutive patients with severe anorexia nervosa or avoidant/restrictive food intake disorder. J Acad Consult Liaison Psychiatry. 65(4):347–356. https://doi.org/10.1016/j.jaclp.2024.02.001

Lee SC, Baranowski ES, Sakremath R, Saraff V, Mohamed Z. 2023. Hypoglycaemia in adrenal insufficiency. Front Endocrinol (Lausanne). 14:1198519. https://doi.org/10.3389/fendo.2023.1198519.

Leehr EJ et al. 2019. Evidence for a sex-specific contribution of polygenic load for anorexia nervosa to body weight and prefrontal brain structure in nonclinical individuals. Neuropsychopharmacology. 44(13):2212–2219. https://doi.org/10.1038/s41386-019-0461-1.

Lehmann CS et al. 2018. The role of objectively measured, altered physical activity patterns for body mass index change during inpatient treatment in female patients with anorexia nervosa. J Clin Med. 7(9):289. https://doi.org/10.3390/jcm7090289

Lehr S et al. 2012. Identification and validation of novel adipokines released from primary human adipocytes. Mol Cell Proteom. 11(1):M111.010504. https://doi.org/10.1074/mcp.M111.010504

Leppanen J, Ng KW, Tchanturia K, Treasure J. 2017. Meta-analysis of the effects of intranasal oxytocin on interpretation and expression of emotions. Neurosci Biobehav Rev. 78:125–144. https://doi.org/10.1016/j.neubiorev.2017.04.010

Leppanen J, Sedgewick F, Cardi V, Treasure J, Tchanturia K. 2019. Cortical morphometry in anorexia nervosa: an out-of-sample replication study. Eur Eat Disord Rev. 27(5):507–520. https://doi.org/10.1002/erv.2686

Lesinskiene S, Barkus A, Ranceva N, Dembinskas A. 2008. A meta-analysis of heart rate and QT interval alteration in anorexia nervosa. World J Biol Psychiatry. 9(2):86–91. https://doi.org/10.1080/15622970701230963

Leuba G et al. 2008. Postsynaptic density protein PSD-95 expression in Alzheimer's disease and okadaic acid induced neuritic retraction. Neurobiol Dis. 30(3):408–419. https://doi.org/10.1016/j.nbd.2008.02.012.

Lewczuk P et al. 2018a. Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease. Alzheimers Res Ther. 10(1):71. 10. https://doi.org/10.1186/s13195-018-0404-9

Lewczuk P et al. 2018b. Cerebrospinal fluid and blood biomarkers for neurodegenerative dementias: an update of the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry. World J Biol Psychiatry. 19(4):244–328. https://doi.org/10.1080/15622975.2017.1375556

Li C et al. 2021. Leptin regulates exon-specific transcription of the Bdnf gene via epigenetic modifications mediated by an AKT/p300 HAT cascade. Mol Psychiatry. 26(8):3701–3722. https://doi.org/10.1038/s41380-020-00922-0

Li D et al. 2017. A genome-wide association study of anorexia nervosa suggests a risk locus implicated in dysregulated leptin signaling. Sci Rep. 7(1):3847. https://doi.org/10.1038/s41598-017-01674-8

Li Y. 2021. Modern epigenetics methods in biological research. Methods. 187:104–113. https://doi.org/10.1016/j.ymeth.2020.06.022

Lim M et al. 2023. Exploring the relationship between disordered sleep and mood in male anorexia nervosa: an actigraphy study. Nutrients. 15(9):2176. https://doi.org/10.3390/nu15092176

Lin J et al. 2022. Dehydroepiandrosterone status and efficacy of dehydroepiandrosterone supplementation for bone health in anorexia nervosa: a systematic review and meta-analysis. Int J Eat Disord. 55(6):733–746. https://doi.org/10.1002/eat.23714

Linardon J et al. 2025. Smartphone digital phenotyping in mental health disorders: a review of raw sensors utilized, machine learning processing pipelines, and derived behavioral features. Psychiatry Res. 348:116483. https://doi.org/10.1016/j.psychres.2025.116483

Linardon J, Torous J. 2025. Integrating artificial intelligence and smartphone technology to enhance personalized assessment and treatment for eating disorders. Int J Eat Disord. 58(8):1415–1424. https://doi.org/10.1002/eat.24468

Liu C et al. 2021. Cytokines: from clinical significance to quantification. Adv Sci. 8(15):2004433. https://doi.org/10.1002/advs.202004433

Liu PZ, Nusslock R. 2018. Exercise-mediated neurogenesis in the hippocampus via BDNF. Front Neurosci. 12:52. https://doi.org/10.3389/fnins.2018.00052

Liu X-f et al. 2023. Regulation of short-chain fatty acids in the immune system [Mini Review]. Front Immunol. 14:1290414. 2023https://doi.org/10.3389/fimmu.2023.1186892

Lloyd EC. 2022. Large-scale analysis of brain morphometry in anorexia nervosa. Biol Psychiatry. 92(9):e41–e42. https://doi.org/10.1016/j.biopsych.2022.07.026

Lloyd EC et al. 2023. Large-scale exploration of whole-brain structural connectivity in anorexia nervosa: alterations in the connectivity of frontal and subcortical networks. Biol Psychiatry Cogn Neurosci Neuroimaging. 8(8):864–873. https://doi.org/10.1016/j.bpsc.2022.06.002

Lo Sauro C, Ravaldi C, Cabras PL, Faravelli C, Ricca V. 2008. Stress, hypothalamic-pituitary-adrenal axis and eating disorders. Neuropsychobiology. 57(3):95–115. https://doi.org/10.1159/000138912

Loos RJF. 2020. 15 years of genome-wide association studies and no signs of slowing down. Nat Commun. 11(1):5900. https://doi.org/10.1038/s41467-020-19653-5

Lopes MP et al. 2022. Associations between bone mineral density, body composition and amenorrhoea in females with eating disorders: a systematic review and meta-analysis. J Eat Disord. 10(1):173. https://doi.org/10.1186/s40337-022-00694-8

Loprinzi PD, Frith E. 2019. A brief primer on the mediational role of BDNF in the exercise-memory link. Clin Physiol Funct Imaging. 39(1):9–14. https://doi.org/10.1111/cpf.12522

Lotter LD et al. 2021. Recovery-associated resting-state activity and connectivity alterations in anorexia nervosa. Biol Psychiatry Cogn Neurosci Neuroimaging. 6(10):1023–1033. https://doi.org/10.1016/j.bpsc.2021.03.006

Lu X, Liu Y, Hao L, Li J, Hua L. 2025. Effects of probiotic supplementation on intestinal flora, brain–gut peptides and clinical

outcomes in children with anorexia nervosa. Br J Nutr. 133(4):491–496. https://doi.org/10.1017/S0007114525000169
Lucas AR, Melton LJ, III, Crowson CS, O'Fallon WM. 1999. Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. Mayo Clin Proc. 74(10):972–977. https://doi.org/10.1016/S0025-6196(11)63994-3
Lucas N et al. 2019. Immunoglobulin G modulation of the melanocortin 4 receptor signaling in obesity and eating disorders. Transl Psychiatry. 9(1):87. https://doi.org/10.1038/s41398-019-0422-9
M'Kadmi C. l et al. 2019. N-terminal liver-expressed antimicrobial peptide 2 (LEAP2) region exhibits inverse agonist activity toward the ghrelin receptor. J Med Chem. 62(2):965–973. https://doi.org/10.1021/acs.jmedchem.8b01644
Mack I et al. 2016. Weight gain in anorexia nervosa does not ameliorate the faecal microbiota, branched chain fatty acid profiles, and gastrointestinal complaints. Sci Rep. 6(1):26752. https://doi.org/10.1038/srep26752
Mack I et al. 2018. Is the impact of starvation on the gut microbiota specific or unspecific to anorexia nervosa? A narrative review based on a systematic literature search. Curr Neuropharmacol. 16(8):1131–1149. https://doi.org/10.2174/1570159X16666180118101354
MacLeod L et al. 2021. A mobile sensing app to monitor youth mental health: observational pilot study. JMIR Mhealth Uhealth. 9(10):e20638. https://doi.org/10.2196/20638
Maguire S et al. 2024. A phase II randomised controlled trial of intranasal oxytocin in anorexia nervosa. Psychoneuroendocrinology. 164:107032. https://doi.org/10.1016/j.psyneuen.2024.107032
Maguire S, O'Dell A, Touyz L, Russell J. 2013. Oxytocin and anorexia nervosa: a review of the emerging literature. Eur Eat Disord Rev. 21(6):475–478. https://doi.org/10.1002/erv.2252
Maïmoun L et al. 2020. Specific effects of anorexia nervosa and obesity on bone mineral density and bone turnover in young women. J Clin Endocrinol Metab. 105(4):e1536–e1548. https://doi.org/10.1210/clinem/dgz259
Maïmoun L et al. 2014. Role of sclerostin and dickkopf-1 in the dramatic alteration in bone mass acquisition in adolescents and young women with recent anorexia nervosa. J Clin Endocrinol Metab. 99(4):E582–590. https://doi.org/10.1210/jc.2013-2565
Maïmoun L et al. 2022. In patients with anorexia nervosa, myokine levels are altered but are not associated with bone mineral density loss and bone turnover alteration. Endocr Connect. 11(5) https://doi.org/10.1530/ec-21-0488
Mancuso C et al. 2020. Changes in appetite-regulating hormones following food intake are associated with changes in reported appetite and a measure of hedonic eating in girls and young women with anorexia nervosa. Psychoneuroendocrinology. 113:104556. https://doi.org/10.1016/j.psyneuen.2019.104556
Mandelkow EM, Mandelkow E. 2012. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harb Perspect Med. 2(7):a006247–a006247. https://doi.org/10.1101/cshperspect.a006247
Mani BK et al. 2019. LEAP2 changes with body mass and food intake in humans and mice. J Clin Invest. 129(9):3909–3923. https://doi.org/10.1172/JCI125332
Mann ER, Lam YK, Uhlig HH. 2024. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol. 24(8):577–595. https://doi.org/10.1038/s41577-024-01014-8
Mansour L S, Tian Y, Yeo BTT, Cropley V, Zalesky A. 2021. High-resolution connectomic fingerprints: mapping neural identity and behavior. Neuroimage. 229:117695. https://doi.org/10.1016/j.neuroimage.2020.117695
Marek S et al. 2022. Reproducible brain-wide association studies require thousands of individuals. Nature. 603(7902):654–660. https://doi.org/10.1038/s41586-022-04492-9
Mathiak K et al. 1999. Serum leptin levels, body fat deposition, and weight in females with anorexia or bulimia nervosa. Horm Metab Res. 31(4):274–277. https://doi.org/10.1055/s-2007-978732
Matochik JA et al. 2005. Effect of leptin replacement on brain structure in genetically leptin-deficient adults. J Clin Endocrinol Metab. 90(5):2851–2854. https://doi.org/10.1210/jc.2004-1979
Matthews VB et al. 2009. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia. 52(7):1409–1418. https://doi.org/10.1007/s00125-009-1364-1
McCarthy TL, Centrella M, Canalis E. 1990. Cortisol inhibits the synthesis of insulin-like growth factor-I in skeletal cells. Endocrinology. 126(3):1569–1575. https://doi.org/10.1210/endo-126-3-1569
McEwen BS, Wingfield JC. 2003. The concept of allostasis in biology and biomedicine. Horm Behav. 43(1):2–15. https://doi.org/10.1016/s0018-506x(02)00024-7
Medicine SfAHa. 2022. Refeeding hypophosphatemia in hospitalized adolescents with anorexia nervosa. J Adolesc Health. 71(4):517–520. https://doi.org/10.1016/j.jadohealth.2022.06.025
Mehler PS et al. 2018. Medical findings in 1,026 consecutive adult inpatient-residential eating disordered patients. Int J Eat Disord. 51(4):305–313. https://doi.org/10.1002/eat.22830
Mehler PS, Walsh K. 2016. Electrolyte and acid-base abnormalities associated with purging behaviors. Int J Eat Disord. 49(3):311–318. https://doi.org/10.1002/eat.22503.
Mehler PS, Watters A, Joiner T, Krantz MJ. 2022. What accounts for the high mortality of anorexia nervosa? Int J Eat Disord. 55(5):633–636. https://doi.org/10.1002/eat.23664
Melbye S, Kessing LV, Bardram JE, Faurholt-Jepsen M. 2020. Smartphone-based self-monitoring, treatment, and automatically generated data in children, adolescents, and young adults with psychiatric disorders: systematic review. JMIR Ment Health. 7(10):e17453. https://doi.org/10.2196/17453
Membrives S et al. 2021. Tracking temporal response dynamics in the ventral striatum during social feedback in anorexia nervosa: a functional magnetic resonance imaging exploratory study. Int J Eat Disord. 54(10):1881–1886. https://doi.org/10.1002/eat.23604
Meneguzzo P, Collantoni E, Solmi M, Tenconi E, Favaro A. 2019. Anorexia nervosa and diffusion weighted imaging: an open methodological question raised by a systematic review and a fractional anisotropy anatomical likelihood estimation meta-analysis. Int J Eat Disord. 52(11):1237–1250. https://doi.org/10.1002/eat.23160
Mercader JM et al. 2007. Blood levels of brain-derived neurotrophic factor correlate with several psychopathological symptoms in anorexia nervosa patients. Neuropsychobiology. 56(4):185–190. https://doi.org/10.1159/000120623
Michalicova A, Majerova P, Kovac A. 2020. Tau protein and its role in blood–brain barrier dysfunction [review]. Front Mol

Neurosci. 13:570045. https://doi.org/10.3389/fnmol.2020.570045
Miller ML, Sanzari CM, Timko CA, Hormes JM. 2023. Impact of virtual adjunctive cognitive remediation therapy on cognitive flexibility and treatment outcomes in comorbid anorexia nervosa and exercise dependence as quantified using novel biomarkers: a stage 1 registered report. Int J Eat Disord. 56(7):1449–1460. https://doi.org/10.1002/eat.23942
Milos G et al. 2020. Short-term metreleptin treatment of patients with anorexia nervosa: rapid on-set of beneficial cognitive, emotional, and behavioral effects. Transl Psychiatry. 10(1):303. https://doi.org/10.1038/s41398-020-00977-1
Minor RK, Chang JW, De Cabo R. 2009. Hungry for life: how the arcuate nucleus and neuropeptide Y may play a critical role in mediating the benefits of calorie restriction. Mol Cell Endocrinol. 299(1):79–88. https://doi.org/10.1016/j.mce.2008.10.044
Miranda M, Morici JF, Zanoni MB, Bekinschtein P. 2019. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. Front Cell Neurosci. 13:363. https://doi.org/10.3389/fncel.2019.00363
Miranda-Olivos R et al. 2023. Exploring the influence of circulating endocannabinoids and nucleus accumbens functional connectivity on anorexia nervosa severity. Mol Psychiatry. 28(11):4793–4800. https://doi.org/10.1038/s41380-023-02253-2
Misra M et al. 2004. Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls. Pediatrics. 114(6):1574–1583. https://doi.org/10.1542/peds.2004-0540
Misra M, Klibanski A. 2014. Endocrine consequences of anorexia nervosa. Lancet Diabetes Endocrinol. 2(7):581–592. https://doi.org/10.1016/s2213-8587(13)70180-3
Misra M et al. 2006. Elevated peptide YY levels in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab. 91(3):1027–1033. https://doi.org/10.1210/jc.2005-1878
Miyata N et al. 2021. Metabolomics profile of Japanese female patients with restricting-type anorexia nervosa. Physiol Behav. 228:113204. https://doi.org/10.1016/j.physbeh.2020.113204
Mogavero MP, Godos J, Grosso G, Caraci F, Ferri R. 2023. Rethinking the role of orexin in the regulation of REM sleep and appetite. Nutrients. 15(17):3679. https://doi.org/10.3390/nu15173679
Mohammadi S, Moosaie F, Saghazadeh A, Mahmoudi M, Rezaei N. 2021. Metabolic profile in patients with narcolepsy: a systematic review and meta-analysis. Sleep Med. 81:268–284. https://doi.org/10.1016/j.sleep.2021.02.040
Mollon J, Almasy L, Jacquemont S, Glahn DC. 2023. The contribution of copy number variants to psychiatric symptoms and cognitive ability. Mol Psychiatry. 28(4):1480–1493. https://doi.org/10.1038/s41380-023-01978-4
Monssen D et al. 2024. The United Kingdom eating disorders genetics initiative. Int J Eat Disord. 57(5):1145–1159. https://doi.org/10.1002/eat.24037
Monteleone A et al. 2016a. Ghrelin response to hedonic eating in underweight and short-term weight restored patients with anorexia nervosa. Psychiatry Res. 235:55–60. https://doi.org/10.1016/j.psychres.2015.12.001
Monteleone AM et al. 2020. Multiple levels assessment of the RDoC "system for social process" in Eating Disorders: biological, emotional and cognitive responses to the Trier Social Stress Test. J Psychiatr Res. 130:160–166. Elsevier Science. https://doi.org/10.1016/j.jpsychires.2020.07.039]
Monteleone AM et al. 2015. Deranged endocannabinoid responses to hedonic eating in underweight and recently weight-restored patients with anorexia nervosa. Am J Clin Nutr. 101(2):262–269. https://doi.org/10.3945/ajcn.114.096164
Monteleone AM et al. 2017. Differences in cortisol awakening response between binge-purging and restrictive patients with anorexia nervosa. Eur Eat Disord Rev. 25(1):13–18. https://doi.org/10.1002/erv.2485
Monteleone AM et al. 2016b. Underweight subjects with anorexia nervosa have an enhanced salivary cortisol response not seen in weight restored subjects with anorexia nervosa. Psychoneuroendocrinology. 70:118–121. https://doi.org/10.1016/j.psyneuen.2016.05.004
Monteleone AM, Treasure J, Kan C, Cardi V. 2018. Reactivity to interpersonal stress in patients with eating disorders: a systematic review and meta-analysis of studies using an experimental paradigm. Neurosci Biobehav Rev. 87:133–150. https://doi.org/10.1016/j.neubiorev.2018.02.002
Monteleone AM et al. 2021a. Multi-omics data integration in anorexia nervosa patients before and after weight regain: a microbiome-metabolomics investigation. Clin Nutr. 40(3):1137–1146. https://doi.org/10.1016/j.clnu.2020.07.021
Monteleone AM et al. 2021b. The gut microbiome and metabolomics profiles of restricting and binge-purging type anorexia nervosa. Nutrients. 13(2):507. https://doi.org/10.3390/nu13020507
Monteleone P et al. 2005. Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa. Neuropsychopharmacology. 30(6):1216–1221. https://doi.org/10.1038/sj.npp.1300695
Monteleone P et al. 2021c. Metabolomics signatures of acutely ill and short-term weight recovered women with anorexia nervosa. Mol Psychiatry. 26(8):3980–3991. https://doi.org/10.1038/s41380-019-0573-3
Monteleone P et al. 2012. Hedonic eating is associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoyl-glycerol in healthy humans: a pilot study. J Clin Endocrinol Metab. 97(6):E917–E924. https://doi.org/10.1210/jc.2011-3018
Monteleone P, Serritella C, Martiadis V, Scognamiglio P, Maj M. 2008. Plasma obestatin, ghrelin, and ghrelin/obestatin ratio are increased in underweight patients with anorexia nervosa but not in symptomatic patients with bulimia nervosa. J Clin Endocrinol Metab. 93(11):4418–4421. https://doi.org/10.1210/jc.2008-1138
Monzon BM et al. 2017. Grey matter volume in adolescents with anorexia nervosa and associated eating disorder symptoms. Eur J Neurosci. 46(7):2297–2307. https://doi.org/10.1111/ejn.13659
Morita C et al. 2015. Gut dysbiosis in patients with anorexia nervosa. PLoS One. 10(12):e0145274. https://doi.org/10.1371/journal.pone.0145274
Moriya J, Takimoto Y, Yoshiuchi K, Shimosawa T, Akabayashi A. 2006. Plasma agouti-related protein levels in women with anorexia nervosa. Psychoneuroendocrinology. 31(9):1057–1061. https://doi.org/10.1016/j.psyneuen.2006.06.006
Mueller RL et al. 2021. Tau: a signaling hub protein [review]. Front Mol Neurosci. 14:647054. https://doi.org/10.3389/fnmol.2021.647054

Mumford J et al. 2019. Long-term outcomes of adolescent anorexia nervosa on bone. J Adolesc Health. 64(3):305–310. https://doi.org/10.1016/j.jadohealth.2018.07.025

Muratore AF et al. 2024. Reduced dorsal fronto-striatal connectivity at rest in anorexia nervosa. Psychol Med. 54(9):2200–2209. https://doi.org/10.1017/S003329172400031X

Murray GK et al. 2021. Could polygenic risk scores be useful in psychiatry?: a review. JAMA Psychiatry. 78(2):210–219. https://doi.org/10.1001/jamapsychiatry.2020.3042

Nagata JM et al. 2019. Comparisons of bone density and body composition among adolescents with anorexia nervosa and atypical anorexia nervosa. Int J Eat Disord. 52(5):591–596. https://doi.org/10.1002/eat.23048

Nakabayashi K et al. 2009. Identification of novel candidate loci for anorexia nervosa at 1q41 and 11q22 in Japanese by a genome-wide association analysis with microsatellite markers. J Hum Genet. 54(9):531–537. https://doi.org/10.1038/jhg.2009.74

Nakahara T et al. 2007. Incomplete restoration of the secretion of ghrelin and PYY compared to insulin after food ingestion following weight gain in anorexia nervosa. J Psychiatr Res. 41(10):814–820. https://doi.org/10.1016/j.jpsychires.2006.07.021

Nakazato M et al. 2009. Brain-derived neurotrophic factor (BDNF) and set-shifting in currently ill and recovered anorexia nervosa (AN) patients. Psychol Med. 39(6):1029–1035. https://doi.org/10.1017/S0033291708004108

Neuman H, Debelius JW, Knight R, Koren O. 2015. Microbial endocrinology: the interplay between the microbiota and the endocrine system. FEMS Microbiol Rev. 39(4):509–521. https://doi.org/10.1093/femsre/fuu010

Nguyen N et al. 2019. Food-intake normalization of dysregulated fatty acids in women with anorexia nervosa. Nutrients. 11(9):2208. https://doi.org/10.3390/nu11092208.

Ni G et al. 2019. The genetic relationship between female reproductive traits and six psychiatric disorders. Sci Rep. 9(1):12041. https://doi.org/10.1038/s41598-019-48403-x.

Niederau C et al. 2025. The influence of anorexia nervosa on oral health and related parameters potentially relevant to orthodontic treatment: a systematic review and meta-analysis. Clin Oral Investig. 29(1):76. https://doi.org/10.1007/s00784-024-05774-4

Nikolova VL et al. 2021. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. JAMA Psychiatry. 78(12):1343–1354. https://doi.org/10.1001/jamapsychiatry.2021.2573

Nilsson IA et al. 2020. Aberrant inflammatory profile in acute but not recovered anorexia nervosa. Brain Behav Immun. 88:718–724. https://doi.org/10.1016/j.bbi.2020.05.024

Nilsson IAK et al. 2019. Plasma neurofilament light chain concentration is increased in anorexia nervosa. Transl Psychiatry. 9(1):180. https://doi.org/10.1038/s41398-019-0518-2

Nishi K et al. 2023. Branched-chain keto acids inhibit mitochondrial pyruvate carrier and suppress gluconeogenesis in hepatocytes. Cell Rep. 42(6):112641. https://doi.org/10.1016/j.celrep.2023.112641

Nova E et al. 2006. Effects of a nutritional intervention with yogurt on lymphocyte subsets and cytokine production capacity in anorexia nervosa patients. Eur J Nutr. 45(4):225–233. https://doi.org/10.1007/s00394-006-0589-8

O'Connor G, Nicholls D. 2013. Refeeding hypophosphatemia in adolescents with anorexia nervosa: a systematic review. Nutr Clin Pract. 28(3):358–364. https://doi.org/10.1177/0884533613476892

O'Neil ME et al. 2016. Reliability and validity of objective measures of physical activity in youth with cerebral palsy who are ambulatory. Phys Ther. 96(1):37–45. https://doi.org/10.2522/ptj.20140201

Ohwada R, Hotta M, Oikawa S, Takano K. 2006. Etiology of hypercholesterolemia in patients with anorexia nervosa. Int J Eat Disord. 39(7):598–601. https://doi.org/10.1002/eat.20298

Onnela JP. 2021. Opportunities and challenges in the collection and analysis of digital phenotyping data. Neuropsychopharmacology. 46(1):45–54. https://doi.org/10.1038/s41386-020-0771-3

World Health Organization. 2024. Clinical descriptions and diagnostic requirements for ICD-11 mental. In: Behavioural and neurodevelopmental disorders. World Health Organization.

Østergaard SD. 2025. Generative artificial intelligence chatbots and delusions: from guesswork to emerging cases. Acta Psychiatr Scand. 152(4):257–259. https://doi.org/10.1111/acps.70022

Ostrowska Z et al. 2016. Vaspin and selected indices of bone status in girls with anorexia nervosa. Endokrynol Pol. 67(6):599–606. https://doi.org/10.5603/EP.2016.0070

Ostrowska Z et al. 2014. Bone metabolism, osteoprotegerin, receptor activator of nuclear factor-kB ligand and selected adipose tissue hormones in girls with anorexia nervosa. Endokrynol Pol. 65(1):33–39. https://doi.org/10.5603/EP.2014.0005

Oświęcimska J et al. 2016. Serum vaspin concentrations in girls with anorexia nervosa. J Pediatr Endocrinol Metab. 29(6):681–686. https://doi.org/10.1515/jpem-2015-0390

Otto B et al. 2007. Peptide YY release in anorectic patients after liquid meal. Appetite. 48(3):301–304. https://doi.org/10.1016/j.appet.2006.06.008

Palacios JE et al. 2024. Effects of a digital therapeutic adjunct to eating disorder treatment on health care service utilization and clinical outcomes: retrospective observational study using electronic health records. JMIR Ment Health. 11:e59145. https://doi.org/10.2196/59145

Pałasz A et al. 2021. Longitudinal study on novel neuropeptides phoenixin, spexin and kisspeptin in adolescent inpatients with anorexia nervosa–association with psychiatric symptoms. Nutr Neurosci. 24(11):896–906. https://doi.org/10.1080/1028415X.2019.1692494

Papini NM et al. 2024. Interplay of polygenic liability with birth-related, somatic, and psychosocial factors in anorexia nervosa risk: a nationwide study. Psychol Med. 54(9):2073–2086. https://doi.org/10.1017/S0033291724000175

Pardo M et al. 2014. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int J Endocrinol. 2014(1):857270–857279. https://doi.org/10.1155/2014/857270

Paslakis G et al. 2019. Associations between neuropsychological performance and appetite-regulating hormones in anorexia nervosa and healthy controls: ghrelin's putative role as a mediator of decision-making. Mol Cell Endocrinol. 497:110441. https://doi.org/10.1016/j.mce.2019.04.021

Pastor A et al. 2016. A lower olfactory capacity is related to higher circulating concentrations of endocannabinoid 2-arachidonoylglycerol and higher body mass index in women. PLoS One. 11(2):e0148734. https://doi.org/10.1371/journal.pone.0148734

Paszynska E et al. 2020a. Salivary opiorphin levels in anorexia nervosa: a case-control study. World J Biol Psychiatry. 21(3):212–219. https://doi.org/10.1080/15622975.2018.1517948
Paszynska E, Dmitrzak-Weglarz M, Tyszkiewicz-Nwafor M, Slopien A. 2016. Salivary alpha-amylase, secretory IgA and free cortisol as neurobiological components of the stress response in the acute phase of anorexia nervosa. World J Biol Psychiatry. 17(4):266–273. https://doi.org/10.3109/15622975.2016.1163419
Paszynska E et al. 2022. Expression of salivary immunoglobulins and their association with analgesic neuropeptide opiorphin in anorexia nervosa during adolescence. J Eat Disord. 10(1):118. https://doi.org/10.1186/s40337-022-00637-3
Paszynska E et al. 2020b. Is there a link between stress and immune biomarkers and salivary opiorphin in patients with a restrictive-type of anorexia nervosa? World J Biol Psychiatry. 21(3):220–229. https://doi.org/10.1080/15622975.2019.1593502
Paszynska E et al. 2018. Study of salivary and serum vaspin and total antioxidants in anorexia nervosa. Clin Oral Investig. 22(8):2837–2845. https://doi.org/10.1007/s00784-018-2370-9
Patrick L. 2002. Eating disorders: a review of the literature with emphasis on medical complications and clinical nutrition. Altern Med Rev. 7(3):184–202. https://doi.org/10.1002/erv.495
Pavlacic JM, Young J, Hahn CK, Ruggiero KJ, Rheingold AA. 2025. Just-in-time adaptive ecological momentary assessment and ecological momentary interventions for posttraumatic psychopathology in the modern age of technology. Psychol Trauma. 17(Suppl 1):S168–S175. https://doi.org/10.1037/tra0001869
Peixoto P, Cartron P-F, Serandour AA, Hervouet E. 2020. From 1957 to nowadays: a brief history of epigenetics. Int J Mol Sci. 21(20):7571. https://doi.org/10.3390/ijms21207571
Perello M, Raingo J. 2013. Leptin activates oxytocin neurons of the hypothalamic paraventricular nucleus in both control and diet-induced obese rodents. PLoS One. 8(3):e59625. https://doi.org/10.1371/journal.pone.0059625
Perino A et al. 2021. Central anorexigenic actions of bile acids are mediated by TGR5. Nat Metab. 3(5):595–603. https://doi.org/10.1038/s42255-021-00398-4.
Peschel SKV et al. 2023. Temporal associations between experiential avoidance and disordered eating behaviors in adolescents and young adults: findings from an epidemiological cohort study with ecological momentary assessment. Eat Weight Disord. 28(1):58. https://doi.org/10.1007/s40519-023-01584-x
Pfluger P et al. 2007. Effect of human body weight changes on circulating levels of peptide YY and peptide YY3–36. J Clin Endocrinol Metab. 92(2):583–588. https://doi.org/10.1210/jc.2006-1425
Philipp E, Pirke K-M, Kellner MB, Krieg J-C. 1991. Disturbed cholecystokinin secretion in patients with eating disorders. Life Sci. 48(25):2443–2450. https://doi.org/10.1016/0024-3205(91)90379-p
Phillipou A, Beilharz F. 2019. Should we shed the weight criterion for anorexia nervosa? Aust N Z J Psychiatry. 53(6):501–502. https://doi.org/10.1177/0004867418814958
Phillipou A, Rossell SL, Castle DJ, Gurvich C, Abel LA. 2014. Square wave jerks and anxiety as distinctive biomarkers for anorexia nervosa. Invest Ophthalmol Vis Sci. 55(12):8366–8370. https://doi.org/10.1167/iovs.14-15807
Piccolo M et al. 2020. Altered circulating endocannabinoids in anorexia nervosa during acute and weight-restored phases: a pilot study. Eur Eat Disord Rev. 28(1):46–54. https://doi.org/10.1002/erv.2709
Pinheiro AP et al. 2010. Association study of 182 candidate genes in anorexia nervosa. Am J Med Genet B Neuropsychiatr Genet. 153B(5):1070–1080. https://doi.org/10.1002/ajmg.b.31082
Pirke KM, Friess E, Kellner MB, Krieg JC, Fichter MM. 1994. Somatostatin in eating disorders. Int J Eat Disord. 15(1):99–102. https://doi.org/10.1002/1098-108X(199401)15:1<99::AID-EAT2260150112>3.0.CO;2-X
Pius-Sadowska E, Machaliński B. 2017. BDNF—a key player in cardiovascular system. J Mol Cell Cardiol. 110:54–60. https://doi.org/10.1016/j.yjmcc.2017.07.007
Plessow F, Eddy KT, Lawson EA. 2018. The Neuropeptide Hormone Oxytocin in Eating Disorders. Curr Psychiatry Rep. 20(10):91. https://doi.org/10.1007/s11920-018-0957-0
Plessow F et al. 2022. Low oxytocin levels are broadly associated with more pronounced psychopathology in anorexia nervosa with primarily restricting but not binge/purge eating behavior. Front Endocrinol (Lausanne). 13:1049541. https://doi.org/10.3389/fendo.2022.1049541
Plomin R. 2000. Behavioural genetics in the 21st century. Int J Behav Dev. 24(1):30–34. https://doi.org/10.1080/016502500383449
Podfigurna A, Czyżyk A, Męczekalski B. 2018. Serum kisspeptin levels in patients with anorexia nervosa. Pol Merkur Lekarski. 45(265):24–27.
Podyma B, Parekh K, Güler AD, Deppmann CD. 2021. Metabolic homeostasis via BDNF and its receptors. Trends Endocrinol Metab. 32(7):488–499. https://doi.org/10.1016/j.tem.2021.04.005
Ponzo V, Pellegrini M, Cioffi I, Scaglione L, Bo S. 2021. The refeeding syndrome: a neglected but potentially serious condition for inpatients. A narrative review. Intern Emerg Med. 16(1):49–60. https://doi.org/10.1007/s11739-020-02525-7
Porras-Garcia B et al. 2021. AN-VR-BE. a randomized controlled trial for reducing fear of gaining weight and other eating disorder symptoms in anorexia nervosa through virtual reality-based body exposure. J Clin Med. 10(4):682. https://doi.org/10.3390/jcm10040682
Porras-Segovia A et al. 2020. Smartphone-based ecological momentary assessment (EMA) in psychiatric patients and student controls: a real-world feasibility study. J Affect Disord. 274:733–741. https://doi.org/10.1016/j.jad.2020.05.067
Preiser JC et al. 2021. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. Crit Care. 25(1):424. https://doi.org/10.1186/s13054-021-03847-4
Prochazkova P et al. 2021. The intestinal microbiota and metabolites in patients with anorexia nervosa. Gut Microbes. 13(1):1–25. https://doi.org/10.1080/19490976.2021.1902771
Prochazkova P et al. 2019. Microbiota, microbial metabolites, and barrier function in a patient with anorexia nervosa after fecal microbiota transplantation. Microorganisms. 7(9):338. https://doi.org/10.3390/microorganisms7090338
Psychiatrists RCo. 2022. Medical emergencies in eating disorders (MEED): Guidance on recognition and management - CR233. https://www.rcpsych.ac.uk/improving-care/campaigning-fo

r-better-mental-health-policy/college-reports/2022-college-reports/cr233
Puckett L. 2023. Renal and electrolyte complications in eating disorders: a comprehensive review. J Eat Disord. 11(1):26. https://doi.org/10.1186/s40337-023-00751-w.
Puckett L, Stein A, Kelley M, Mehler PS. 2024. Evaluation of mean plasma glucose levels using HbA1C in patients with severe eating disorders. Int J Eat Disord. 57(12):2469–2474. https://doi.org/10.1002/eat.24285
Qian XB et al. 2020. A guide to human microbiome research: study design, sample collection, and bioinformatics analysis. Chin Med J (Engl). 133(15):1844–1855. https://doi.org/10.1097/cm9.0000000000000871
Quesnel DA, Cooper M, Fernandez-Del-Valle M, Reilly A, Calogero RM. 2023. Medical and physiological complications of exercise for individuals with an eating disorder: a narrative review. J Eat Disord. 11(1):3. https://doi.org/10.1186/s40337-022-00685-9
Rabl M et al. 2024. Plasma neurofilament light, glial fibrillary acid protein, and phosphorylated tau 181 as biomarkers for neuropsychiatric symptoms and related clinical disease progression. Alzheimers Res Ther. 16(1):165. https://doi.org/10.1186/s13195-024-01526-4
Raevuori A et al. 2014. The increased risk for autoimmune diseases in patients with eating disorders. PLoS One. 9(8):e104845. https://doi.org/10.1371/journal.pone.0104845
Ralph-Nearman C, Osborn KD, Chang RS, Barber KE. 2024. Momentary physiological indices related to eating disorders: a systematic and methodological review. Eur Eat Disord Rev. 32(4):700–717. https://doi.org/10.1002/erv.3062
Ralph-Nearman C, Osborn KD, Chang RS, Barber KE. 2024. Momentary physiological indices related to eating disorders: a systematic and methodological review. Euro Eating Disorders Rev. 32(4):700–717. https://doi.org/10.1002/erv.3062
Recillas-Targa F. 2022. Cancer epigenetics: an overview. Arch Med Res. 53(8):732–740. https://doi.org/10.1016/j.arcmed.2022.11.003
Reed KK et al. 2024. Energy expenditure during nutritional rehabilitation: a scoping review to investigate hypermetabolism in individuals with anorexia nervosa. J Eat Disord. 12(1):63. https://doi.org/10.1186/s40337-024-01019-7
Reville M-C, O'Connor L, Frampton I. 2016. Literature review of cognitive neuroscience and anorexia nervosa. Curr Psychiatry Rep. 18(2):18. https://doi.org/10.1007/s11920-015-0651-4
Riedlinger C et al. 2022. Gastrointestinal complaints in patients with anorexia nervosa in the timecourse of inpatient treatment. Front Psychiatry. 13Article:962837. https://doi.org/10.3389/fpsyt.2022.962837.
Riedlinger C et al. 2020. Which symptoms, complaints and complications of the gastrointestinal tract occur in patients with eating disorders? A systematic review and quantitative analysis. Front Psychiatry. 11:195. https://doi.org/10.3389/fpsyt.2020.00195
Rigaud D, Boulier A, Tallonneau I, Brindisi MC, Rozen R. 2010. Body fluid retention and body weight change in anorexia nervosa patients during refeeding. Clin Nutr. 29(6):749–755. https://doi.org/10.1016/j.clnu.2010.05.007
Riva A, Pigni M, Nacinovich R. 2021. Renal dysfunctions and clinical correlates in adolescents with restrictive anorexia nervosa. Clin Nutr ESPEN. 43:230–234. https://doi.org/10.1016/j.clnesp.2021.04.011
Roberts MA, Thorpe CR, Macgregor DP, Paoletti N, Ierino FL. 2005. Severe renal failure and nephrocalcinosis in anorexia nervosa. Med J Aust. 182(12):635–636. https://doi.org/10.5694/j.1326-5377.2005.tb06851.x
Robinson L, Aldridge V, Clark EM, Misra M, Micali N. 2016. A systematic review and meta-analysis of the association between eating disorders and bone density. Osteoporos Int. 27(6):1953–1966. https://doi.org/10.1007/s00198-015-3468-4
Rosen E, Bakshi N, Watters A, Rosen HR, Mehler PS. 2017. Hepatic Complications of Anorexia Nervosa. Dig Dis Sci. 62(11):2977–2981. https://doi.org/10.1007/s10620-017-4766-9
Rosengren LE, Karlsson JE, Sjögren M, Blennow K, Wallin A. 1999. Neurofilament protein levels in CSF are increased in dementia. Neurology. 52(5):1090–1093. https://doi.org/10.1212/wnl.52.5.1090
Rossi E et al. 2024. The maltreated eco-phenotype of eating disorders: a new diagnostic specifier? A systematic review of the evidence and comprehensive description. Neurosci Biobehav Rev. 160:105619. https://doi.org/10.1016/j.neubiorev.2024.105619
Roubalova R et al. 2021. Altered serum immunological and biochemical parameters and microbiota composition in patients with AN during realimentation. Front Nutr. 8:680870. https://doi.org/10.3389/fnut.2021.680870
Roubalová R et al. 2024. Influence of the gut microbiome on appetite-regulating neuropeptides in the hypothalamus: insight from conventional, antibiotic-treated, and germ-free mouse models of anorexia nervosa. Neurobiol Dis. 193:106460. https://doi.org/10.1016/j.nbd.2024.106460
Rozgonjuk D et al. 2023. Smartphone and Instagram use, body dissatisfaction, and eating disorders: investigating the associations using self-report and tracked data. J Eat Disord. 11(1):149. https://doi.org/10.1186/s40337-023-00865-1
Rubinov M, Sporns O. 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 52(3):1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003
Sala M et al. 2023. Predictors of relapse in eating disorders: a meta-analysis. J Psychiatr Res. 158:281–299. https://doi.org/10.1016/j.jpsychires.2023.01.002
Salehi MA et al. 2021. Serum profiling of anorexia nervosa: a (1) H NMR-based metabolomics study. Eur Neuropsychopharmacol. 49:1–10. https://doi.org/10.1016/j.euroneuro.2021.02.015
Sall H, Timperley J. 2015. Bradycardia in anorexia nervosa. BMJ Case Rep. 2015:bcr2015211273. https://doi.org/10.1136/bcr-2015-211273
Sánchez-Sánchez JL, Rolland Y. 2023. Editorial: social isolation and loneliness: overlooked therapeutic targets of anorexia of aging? J Nutr Health Aging. 27(10):794–796. https://doi.org/10.1007/s12603-023-2011-0
Sandvik P, Lydersen S, Hegstad S, Spigset O. 2020. Association between low body weight and cytochrome P-450 enzyme activity in patients with anorexia nervosa. Pharmacol Res Perspect. 8(3):e00615. https://doi.org/10.1002/prp2.615
Santangelo G et al. 2022. Echocardiographic changes in anorexia nervosa: a pathophysiological adaptation or a disease? Intern Emerg Med. 17(3):777–787. https://doi.org/10.1007/s11739-021-02871-0
Santonastaso P, Sala A, Favaro A. 1998. Water intoxication in anorexia nervosa: a case report. Int J Eat Disord. 24(4):439–442. https://doi.org/10.1002/(sici)1098-108x(199812)24:4<439::aid-eat12>3.0.co;2-4

Santos Ferreira DL et al. 2019. Associations between blood metabolic profile at 7 years old and eating disorders in adolescence: findings from the avon longitudinal study of parents and children. Metabolites. 9(9):191. https://doi.org/10.3390/metabo9090191.

Sartorius A et al. 2009. Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. Pharmacopsychiatry. 42(6):270–276. https://doi.org/10.1055/s-0029-1224162

Sauchelli S et al. 2015. Physical activity in anorexia nervosa: how relevant is it to therapy response? Eur Psychiatry. 30(8):924–931. https://doi.org/10.1016/j.eurpsy.2015.09.008

Sauchelli S et al. 2016. Orexin and sleep quality in anorexia nervosa: clinical relevance and influence on treatment outcome. Psychoneuroendocrinology. 65:102–108. https://doi.org/10.1016/j.psyneuen.2015.12.014

Scaife JC, Godier LR, Filippini N, Harmer CJ, Park RJ. 2017. Reduced resting-state functional connectivity in current and recovered restrictive anorexia nervosa. Front Psychiatry. 8:30. https://doi.org/10.3389/fpsyt.2017.00030

Schafernak KT. 2016. Gelatinous transformation of the bone marrow from anorexia nervosa. Blood. 127(10):1374–1374. https://doi.org/10.1182/blood-2015-11-683946.

Schmalbach I et al. 2020. Cortisol reactivity in patients with anorexia nervosa after stress induction. Transl Psychiatry. 10(1):275. https://doi.org/10.1038/s41398-020-00955-7

Schoretsanitis G et al. 2021. Therapeutic drug monitoring of long-acting injectable antipsychotic drugs. Ther Drug Monit. 43(1):79–102. https://doi.org/10.1097/ftd.0000000000000830

Schorr M, Lawson EA, Dichtel LE, Klibanski A, Miller KK. 2015. Cortisol measures across the weight spectrum. J Clin Endocrinol Metab. 100(9):3313–3321. https://doi.org/10.1210/JC.2015-2078

Schorr M, Miller KK. 2017. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol. 13(3):174–186. https://doi.org/10.1038/nrendo.2016.175

Schulz N et al. 2021. Gut microbiota alteration in adolescent anorexia nervosa does not normalize with short-term weight restoration. Int J Eat Disord. 54(6):969–980. https://doi.org/10.1002/eat.23435

Sedlackova D et al. 2012. Comparison of a high-carbohydrate and high-protein breakfast effect on plasma ghrelin, obestatin, NPY and PYY levels in women with anorexia and bulimia nervosa. Nutr Metab (Lond). 9(1):52. 9. https://doi.org/10.1186/1743-7075-9-52

Sedlackova D et al. 2011. Changes of plasma obestatin, ghrelin and NPY in anorexia and bulimia nervosa patients before and after a high-carbohydrate breakfast. Physiol Res. 60(1):165.

Seeley RJ et al. 1997. Melanocortin receptors in leptin effects. Nature. 390(6658):349–349. https://doi.org/10.1038/37016

Seidel M et al. 2024. Dynamic changes in local brain connectivity and activity: a longitudinal study in adolescent anorexia nervosa. Biol Psychiatry Cogn Neurosci Neuroimaging. 9(4):447–458. https://doi.org/10.1016/j.bpsc.2024.01.006

Seidel M et al. 2015. Serum visfatin concentration in acutely ill and weight-recovered patients with anorexia nervosa. Psychoneuroendocrinology. 53:127–135. https://doi.org/10.1016/j.psyneuen.2014.12.010

Seidel M et al. 2021. A systematic review and meta-analysis finds increased blood levels of all forms of ghrelin in both restricting and binge-eating/purging subtypes of anorexia nervosa. Nutrients. 13(2):709. https://doi.org/10.3390/nu13020709

Seitz J, Herpertz-Dahlmann B, Konrad K. 2016. Brain morphological changes in adolescent and adult patients with anorexia nervosa. J Neural Transm (Vienna). 123(8):949–959. https://doi.org/10.1007/s00702-016-1567-9

Seitz J, Konrad K, Herpertz-Dahlmann B. 2018. Extend, pathomechanism and clinical consequences of brain volume changes in anorexia nervosa. Curr Neuropharmacol. 16(8):1164–1173. https://doi.org/10.2174/1570159X15666171109145651

Seitz J et al. 2024. Long-term dynamics of serum α-MSH and α-MSH-binding immunoglobulins with a link to gut microbiota composition in patients with anorexia nervosa. Neuroendocrinology. 114(10):907–920. https://doi.org/10.1159/000539316

Sekaninova N, Bona Olexova L, Visnovcova Z, Ondrejka I, Tonhajzerova I. 2020. Role of neuroendocrine, immune, and autonomic nervous system in anorexia nervosa-linked cardiovascular diseases. Int J Mol Sci. 21(19):7302. https://doi.org/10.3390/ijms21197302

Shaygannejad A et al. 2024. The role of glial fibrillary acidic protein as a biomarker in multiple sclerosis and neuromyelitis optica spectrum disorder: a systematic review and meta-analysis. Medicina (Kaunas). 60(7):1050. https://doi.org/10.3390/medicina60071050

Shergill KK, Shergill GS, Pillai HJ. 2017. Gelatinous transformation of bone marrow: rare or underdiagnosed? Autops Case Rep. 7(4):8–17. https://doi.org/10.4322/acr.2017.039

Shiffman S, Stone AA, Hufford MR. 2008. Ecological momentary assessment. Annu Rev Clin Psychol. 4(1):1–32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415

Shih PB et al. 2016. Dysregulation of soluble epoxide hydrolase and lipidomic profiles in anorexia nervosa. Mol Psychiatry. 21(4):537–546. https://doi.org/10.1038/mp.2015.26

Shobeiri P et al. 2022. Serum and plasma levels of brain-derived neurotrophic factor in individuals with eating disorders (EDs): a systematic review and meta-analysis. J Eat Disord. 10(1):105. https://doi.org/10.1186/s40337-022-00630-w

Sienkiewicz E et al. 2011. Long-term metreleptin treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women. Metabolism. 60(9):1211–1221. https://doi.org/10.1016/j.metabol.2011.05.016

Silverman JA. 1974. Anorexia nervosa: clinical observations in a successful treatment plan. J Pediatr. 84(1):68–73. https://doi.org/10.1016/s0022-3476(74)80555-x

Simpson CC, Mazzeo SE. 2017. Calorie counting and fitness tracking technology: associations with eating disorder symptomatology. Eat Behav. 26:89–92. https://doi.org/10.1016/j.eatbeh.2017.02.002

Sirufo MM, Magnanimi LM, Ginaldi L, De Martinis M. 2022. Anorexia nervosa and autoimmune comorbidities: a bidirectional route? CNS Neurosci Ther. 28(12):1921–1929. https://doi.org/10.1111/cns.13953

Sjögren M et al. 2001. Neurofilament protein in cerebrospinal fluid: a marker of white matter changes. J Neurosci Res. 66(3):510–516. https://doi.org/10.1002/jnr.1242

Skinner JA, Campbell EJ, Dayas CV, Garg ML, Burrows TL. 2019. The relationship between oxytocin, dietary intake and feeding: a systematic review and meta-analysis of studies in mice and rats. Front Neuroendocrinol. 52:65–78. https://doi.org/10.1016/j.yfrne.2018.09.002

Smith KE et al. 2019. Moving beyond self-report data collection in the natural environment: a review of the past and future directions for ambulatory assessment in eating disorders. Int J Eat Disord. 52(10):1157–1175. https://doi.org/10.1002/eat.23124

Smith KR, Moran TH. 2021. Gastrointestinal peptides in eating-related disorders. Physiol Behav. 238:113456. https://doi.org/10.1016/j.physbeh.2021.113456

Smythe J, Colebourn C, Prisco L, Petrinic T, Leeson P. 2021. Cardiac abnormalities identified with echocardiography in anorexia nervosa: systematic review and meta-analysis. Br J Psychiatry. 219(3):477–486. https://doi.org/10.1192/bjp.2020.1

Socała K et al. 2021. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res. 172:105840. https://doi.org/10.1016/j.phrs.2021.105840

Solinas M, Goldberg SR, Piomelli D. 2008. The endocannabinoid system in brain reward processes. Br J Pharmacol. 154(2):369–383. https://doi.org/10.1038/bjp.2008.130

Solis B et al. 2002. The effect of fermented milk on interferon production in malnourished children and in anorexia nervosa patients undergoing nutritional care [Review. Eur J Clin Nutr. 56(S4):S27–S33. https://doi.org/10.1038/sj.ejcn.1601659

Solmi M et al. 2016. Bone mineral density, osteoporosis, and fractures among people with eating disorders: a systematic review and meta-analysis. Acta Psychiatr Scand. 133(5):341–351. https://doi.org/10.1111/acps.12556

Solmi M et al. 2015. Inflammatory cytokines and anorexia nervosa: a meta-analysis of cross-sectional and longitudinal studies. Psychoneuroendocrinology. 51:237–252. https://doi.org/10.1016/j.psyneuen.2014.09.031

Spadini S, Ferro M, Lamanna J, Malgaroli A. 2021. Activity-based anorexia animal model: a review of the main neurobiological findings. J Eat Disord. 9(1):123. https://doi.org/10.1186/s40337-021-00481-x.

Špilak A et al. 2025. Effects of small extracellular vesicles derived from normoxia- and hypoxia-treated prostate cancer cells on the submandibular salivary gland epithelium in vitro. Tissue Barriers. 13(1):2347062. https://doi.org/10.1080/21688370.2024.2347062

Stalder T et al. 2016. Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology. 63:414–432. https://doi.org/10.1016/j.psyneuen.2015.10.010

Stedal K, Broomfield C, Hay P, Touyz S, Scherer R. 2021. Neuropsychological functioning in adult anorexia nervosa: a meta-analysis. Neurosci Biobehav Rev. 130:214–226. https://doi.org/10.1016/j.neubiorev.2021.08.021

Steiger H, Booij L. 2020. Eating disorders, heredity and environmental activation: getting epigenetic concepts into practice. J Clin Med. 9(5):1332. https://doi.org/10.3390/jcm9051332

Steiger H et al. 2019. A longitudinal, epigenome-wide study of DNA methylation in anorexia nervosa: results in actively ill, partially weight-restored, long-term remitted and non-eating-disordered women. J Psychiatry Neurosci. 44(3):205–213. https://doi.org/10.1503/jpn.170242

Steiger H et al. 2023. DNA methylation in people with anorexia nervosa: epigenome-wide patterns in actively ill, long-term remitted, and healthy-eater women. World J Biol Psychiatry. 24(3):254–259. https://doi.org/10.1080/15622975.2022.2089731

Steiger H, Thaler L. 2016. Eating disorders, gene-environment interactions and the epigenome: roles of stress exposures and nutritional status. Physiol Behav. 162:181–185. https://doi.org/10.1016/j.physbeh.2016.01.041

Steinhäuser JL et al. 2021. Is serum BDNF altered in acute, short-and long-term recovered restrictive type anorexia nervosa? Nutrients. 13(2):432. https://doi.org/10.3390/nu13020432

Stengel A, Giel K. 2023. Emerging therapeutic targets for anorexia nervosa. Expert Opin Ther Targets. 27(4-5):281–292. https://doi.org/10.1080/14728222.2023.2206954

Stengel A et al. 2014. Obese patients have higher circulating protein levels of dipeptidyl peptidase IV. Peptides. 61:75–82. https://doi.org/10.1016/j.peptides.2014.09.006

Stengel A et al. 2013. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity–correlation with body mass index. Peptides. 39:125–130. https://doi.org/10.1016/j.peptides.2012.11.014

Steward T et al. 2022. Dorsolateral prefrontal cortex and amygdala function during cognitive reappraisal predicts weight restoration and emotion regulation impairment in anorexia nervosa. Psychol Med. 52(5):844–852. https://doi.org/10.1017/S0033291720002457

Steward T et al. 2019. Reduced plasma orexin—a concentrations are associated with cognitive deficits in anorexia nervosa. Sci Rep. 9(1):7910. https://doi.org/10.1038/s41598-019-44450-6

Stheneur C, Bergeron S, Lapeyraque AL. 2014. Renal complications in anorexia nervosa. Eat Weight Disord. 19(4):455–460. https://doi.org/10.1007/s40519-014-0138-z

Stierle J et al. 2023. Using smart phone technology to improve daily living skills for individuals with intellectual disabilities. J Appl Res Intellect Disabil. 36(5):1169–1178. https://doi.org/10.1111/jar.13139

Stock S et al. 2005. Ghrelin, peptide YY, glucose-dependent insulinotropic polypeptide, and hunger responses to a mixed meal in anorexic, obese, and control female adolescents. J Clin Endocrinol Metab. 90(4):2161–2168. https://doi.org/10.1210/jc.2004-1251

Su T et al. 2021. Structural and functional brain alterations in anorexia nervosa: a multimodal meta-analysis of neuroimaging studies. Hum Brain Mapp. 42(15):5154–5169. https://doi.org/10.1002/hbm.25602

Suau Q et al. 2024. Current knowledge about ActiGraph GT9X link activity monitor accuracy and validity in measuring steps and energy expenditure: a systematic review. Sensors (Basel). 24(3):825. https://doi.org/10.3390/s24030825

Subramanian R, Khardori R. 2000. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. Medicine (Baltimore). 79(1):1–8. https://doi.org/10.1097/00005792-200001000-00001

Sudmant PH et al. 2015. An integrated map of structural variation in 2,504 human genomes. Nature. 526(7571):75–81. https://doi.org/10.1038/nature15394

Sudo Y et al. 2024. Comprehensive elucidation of resting-state functional connectivity in anorexia nervosa by a multicenter cross-sectional study. Psychol Med. 54(10):2347–2360. https://doi.org/10.1017/S0033291724000485

Sugimoto T, Murata T, Omori M, Wada Y. 2003. Central pontine myelinolysis associated with hypokalaemia in anorexia nervosa. J Neurol Neurosurg Psychiatry. 74(3):353–355. https://doi.org/10.1136/jnnp.74.3.353

Sullivan PF et al. 2018. Psychiatric genomics: an update and an Agenda. Am J Psychiatry. 175(1):15–27. https://doi.org/10.1176/appi.ajp.2017.17030283

Susta M et al. 2022. The sight of one's own body: could qEEG help predict the treatment response in anorexia nervosa? Front Psychol. 13:958501. https://doi.org/10.3389/fpsyg.2022.958501

Swenne I, Larsson PT. 1999. Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersion. Acta Paediatr. 88(3):304–309. https://doi.org/10.1080/08035259950170079

Szyf M. 2015. Nongenetic inheritance and transgenerational epigenetics. Trends Mol Med. 21(2):134–144. https://doi.org/10.1016/j.molmed.2014.12.004

Takagi K et al. 2013. Anti-ghrelin immunoglobulins modulate ghrelin stability and its orexigenic effect in obese mice and humans. Nat Commun. 4(1):2685. https://doi.org/10.1038/ncomms3685

Tam FI et al. 2022. Liver and vitamin B(12) parameters in patients with anorexia nervosa before and after short-term weight restoration. Psychiatry Res. 314:114673. https://doi.org/10.1016/j.psychres.2022.114673.

Tam FI et al. 2021. Adverse effects of refeeding on the plasma lipidome in young individuals with anorexia nervosa? J Am Acad Child Adolesc Psychiatry. 60(12):1479–1490. https://doi.org/10.1016/j.jaac.2021.02.014.

Tam FI et al. 2020. Peptide YY3–36 concentration in acute-and long-term recovered anorexia nervosa. Eur J Nutr. 59(8):3791–3799. https://doi.org/10.1007/s00394-020-02210-7

Tamai H et al. 1993. Changes in plasma cholecystokinin concentrations after oral glucose tolerance test in anorexia nervosa before and after therapy. Metabolism. 42(5):581–584. https://doi.org/10.1016/0026-0495(93)90216-b

Tan BK, Adya R, Randeva HS. 2010. Omentin: a novel link between inflammation, diabesity, and cardiovascular disease. Trends Cardiovasc Med. 20(5):143–148. https://doi.org/10.1016/j.tcm.2010.12.002

Taquet M, Geddes JR, Luciano S, Harrison PJ. 2021. Incidence and outcomes of eating disorders during the COVID-19 pandemic. Br J Psychiatry. 220(5):1–3. https://doi.org/10.1192/bjp.2021.105

Tennoune N et al. 2014. Bacterial ClpB heat-shock protein, an antigen-mimetic of the anorexigenic peptide [alpha]-MSH, at the origin of eating disorders. Transl Psychiatry. 4(10):e458–e458. https://doi.org/10.1038/tp.2014.98

Terashi M et al. 2011. Ghrelin reactive autoantibodies in restrictive anorexia nervosa. Nutrition. 27(4):407–413. https://doi.org/10.1016/j.nut.2011.01.002

Terra X et al. 2013. Adipocytokine levels in women with anorexia nervosa. Relationship with weight restoration and disease duration. Int J Eat Disord. 46(8):855–861. https://doi.org/10.1002/eat.22166

Tey HL, Lim SC, Snodgrass AM. 2005. Refeeding oedema in anorexia nervosa. Singapore Med J. 46(6):308–310.

Thavaraputta S, Ungprasert P, Witchel SF, Fazeli PK. 2023. Anorexia nervosa and adrenal hormones: a systematic review and meta-analysis. Eur J Endocrinol. 189(3):S64–s73. https://doi.org/10.1093/ejendo/lvad123.

Theisen FM et al. 2006. Serum levels of olanzapine and its N-desmethyl and 2-hydroxymethyl metabolites in child and adolescent psychiatric disorders: effects of dose, diagnosis, age, sex, smoking, and comedication. Ther Drug Monit. 28(6):750–759. https://doi.org/10.1097/01.ftd.0000249950.75462.7f

Theofanopoulou C, Andirkó A, Boeckx C, Jarvis ED. 2022. Oxytocin and vasotocin receptor variation and the evolution of human prosociality. Compr Psychoneuroendocrinol. 11:100139. https://doi.org/10.1016/j.cpnec.2022.100139

Thomas B et al. 2025. Enterobacterial caseinolytic protease B (ClpB) and ClpB antibodies in adolescents with anorexia nervosa. J Psychiatr Res. 184:8–16. https://doi.org/10.1016/j.jpsychires.2025.02.034

Thomas, B., Lahaye, E., Wallart, L., do Rego, J. L., do Rego, J. C., & Fetissov, S. O. (2024). Immunoneutralization of enterobacterial ClpB protein protects mice against activity-based anorexia. In: 46th Annual meeting of the French Society of Neuroendocrinology, Nice, France.

Thomaz TG et al. 2024. Treatment of narcolepsy type 1 with orexin: a systematic review. Cureus. 16(12):e76692. https://doi.org/10.7759/cureus.76692

Thornton LM, Mazzeo SE, Bulik CM. 2011. The heritability of eating disorders: methods and current findings. Curr Top Behav Neurosci. 6:141–156. https://doi.org/10.1007/7854_2010_91

Tolwani RJ et al. 2004. BDNF overexpression produces a long-term increase in myelin formation in the peripheral nervous system. J Neurosci Res. 77(5):662–669. https://doi.org/10.1002/jnr.20181

Tomasik PJ, Sztefko K, Starzyk J, Rogatko I, Szafran Z. 2005. Entero-insular axis in children with anorexia nervosa. Psychoneuroendocrinology. 30(4):364–372. https://doi.org/10.1016/j.psyneuen.2004.10.003

Tomášová P et al. 2022. NMR- and MS-based untargeted metabolomic study of stool and serum samples from patients with anorexia nervosa. J Proteome Res. 21(3):778–787. https://doi.org/10.1021/acs.jproteome.1c00537

Torabi A, Reisi J, Kargarfard M, Mansourian M. 2024. Differences in the impact of various types of exercise on irisin levels: a systematic review and meta-analysis. Int J Prev Med. 15:11. https://doi.org/10.4103/ijpvm.ijpvm_76_23

Torous J, Nebeker C. 2017. Navigating ethics in the digital age: introducing connected and open research ethics (CORE), a tool for researchers and institutional review boards. J Med Internet Res. 19(2):e6793. https://doi.org/10.2196/jmir.6793

Tregarthen JP, Lock J, Darcy AM. 2015. Development of a smartphone application for eating disorder self-monitoring. Int J Eat Disord. 48(7):972–982. https://doi.org/10.1002/eat.22386

Tseng MM, Chien LN, Tu CY, Zheng CM, Liu HY. 2023. Risk of dialysis and renal diseases in patients with anorexia nervosa in Taiwan. Int J Eat Disord. 56(5):991–1000. https://doi.org/10.1002/eat.23899

Tsigos C, Chrousos GP. 2002. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 53(4):865–871. https://doi.org/10.1016/s0022-3999(02)00429-4

Tufvesson-Alm M et al. 2024. Decoding the influence of central LEAP2 on food intake and its effect on accumbal dopamine release. Prog Neurobiol. 236:102615. https://doi.org/10.1016/j.pneurobio.2024.102615

Tuli S et al. 2023. Bone density, geometry, structure and strength estimates in adolescent and young adult women with atypical anorexia nervosa versus typical anorexia nervosa and normal-weight healthy controls. Nutrients. 15(18):3946. https://doi.org/10.3390/nu15183946

Tural U, Iosifescu DV. 2022. Adiponectin in anorexia nervosa and its modifiers: a meta-regression study. Int J Eat Disord. 55(10):1279–1290. https://doi.org/10.1002/eat.23753

Türkel İ, Memi G, Yazgan B. 2022. Impact of spexin on metabolic diseases and inflammation: an updated minireview. Exp Biol Med (Maywood). 247(7):567–573. https://doi.org/10.1177/15353702211072443

Turner J, Batik M, Palmer LJ, Forbes D, McDermott BM. 2000. Detection and importance of laxative use in adolescents with anorexia nervosa. J Am Acad Child Adolesc Psychiatry. 39(3):378–385. https://doi.org/10.1097/00004583-200003000-00021

Tyszkiewicz-Nwafor M, Dutkiewicz A, Paszynska E, Dmitrzak-Weglarz M, Slopien A. 2021. Omentin and visfatin in adolescent inpatients with anorexia nervosa; association with symptoms. Neuropeptides. 86:102133. https://doi.org/10.1016/j.npep.2021.102133

Tyszkiewicz-Nwafor M et al. 2021. Neuropeptide Y and peptide YY in association with depressive symptoms and eating behaviours in adolescents across the weight spectrum: from anorexia nervosa to obesity. Nutrients. 13(2):598. https://doi.org/10.3390/nu13020598

Tyszkiewicz-Nwafor M et al. 2020. Brain-derived neurotrophic factor and oxytocin signaling in association with clinical symptoms in adolescent inpatients with anorexia nervosa—a longitudinal study. Front Psychiatry. 10:1032. https://doi.org/10.3389/fpsyt.2019.01032

Tyszkiewicz-Nwafor M, Slopien A, Dmitrzak-Węglarz M, Rybakowski F. 2019. Adiponectin and resistin in acutely ill and weight-recovered adolescent anorexia nervosa: association with psychiatric symptoms. World J Biol Psychiatry. 20(9):723–731. https://doi.org/10.1080/15622975.2018.1492735

Uehara T et al. 2005. Plasma des-acyl and acyl ghrelin in patients with eating disorders. Eat Weight Disord. 10(4):264–266. https://doi.org/10.1007/bf03327494

Uniacke B et al. 2019. Resting-state connectivity within and across neural circuits in anorexia nervosa. Brain Behav. 9(1):e01205. https://doi.org/10.1002/brb3.1205

Unterecker S et al. 2019. Therapeutisches drug-monitoring in der neuropsychopharmakologie. Nervenarzt. 90(5):463–471. https://doi.org/10.1007/s00115-018-0643-9.

Urano A, Hotta M, Ohwada R, Araki M. 2015. Vitamin K deficiency evaluated by serum levels of undercarboxylated osteocalcin in patients with anorexia nervosa with bone loss. Clin Nutr. 34(3):443–448. https://doi.org/10.1016/j.clnu.2014.04.016.

van den Berg JP, Elgersma HJ, Zeillemaker-Hoekstra M. 2023. Anorexia nervosa: practical implications for the anaesthetist. BJA Educ. 23(1):17–23. https://doi.org/10.1016/j.bjae.2022.10.001

Van Den Heuvel MP, Pol HEH. 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol. 20(8):519–534. https://doi.org/10.1016/j.euroneuro.2010.03.008

Vaz-Leal FJ et al. 2018. Blunted cortisol response to stress in patients with eating disorders: its association to bulimic features. Euro Eating Disorders Rev. 26(3):207–216. https://doi.org/10.1002/erv.2581

Verbelen M, Weale ME, Lewis CM. 2017. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? Pharmacogenomics J. 17(5):395–402. https://doi.org/10.1038/tpj.2017.21

Veronese N et al. 2015. Vitamin D status in anorexia nervosa: a meta-analysis. Int J Eat Disord. 48(7):803–813. https://doi.org/10.1002/eat.22370

Via E et al. 2023. Longitudinal study in adolescent anorexia nervosa: evaluation of cortico-striatal and default mode network resting-state brain circuits. Eur Child Adolesc Psychiatry. 32(3):513–526. https://doi.org/10.1007/s00787-021-01880-w

Vinusha BV, Varshitha RM, Nikhitha N, Divya DM. 2023. Smartwatch-based vomiting sensation detection using heart rate analysis and metaverse integration. In: 2023 14th International Conference on Computing Communication and Networking Technologies (ICCCNT), 6–8 July 2023. https://doi.org/10.1109/ICCCNT56998.2023.10306491

von Schnurbein J et al. 2023. Positive effect of leptin substitution on mood and behaviour in patients with congenital leptin deficiency. Pediatr Obes. 18(8):e13057. https://doi.org/10.1111/ijpo.13057.

Wabitsch M et al. 2001. Serum leptin, gonadotropin, and testosterone concentrations in male patients with anorexia nervosa during weight gain. J Clin Endocrinol Metab. 86(7):2982–2988. https://doi.org/10.1210/jcem.86.7.7685

Wada S, Nagase T, Koike Y, Kugai N, Nagata N. 1992. A case of anorexia nervosa with acute renal failure induced by rhabdomyolysis; possible involvement of hypophosphatemia or phosphate depletion. Intern Med. 31(4):478–482. https://doi.org/10.2169/internalmedicine.31.478

Wade TD et al. 2013a. Genetic variants associated with disordered eating. Int J Eat Disord. 46(6):594–608. https://doi.org/10.1002/eat.22133

Wade TD et al. 2013b. A study of changes in genetic and environmental influences on weight and shape concern across adolescence. J Abnorm Psychol. 122(1):119–130. https://doi.org/10.1037/a0030290

Walder A, Baumann P. 2008. Increased creatinine kinase and rhabdomyolysis in anorexia nervosa. Int J Eat Disord. 41(8):766–767. https://doi.org/10.1002/eat.20548

Walker A et al. 2025. Genome-wide copy number variation association study in anorexia nervosa. Mol Psychiatry. 30(5):2009–2016. https://doi.org/10.1038/s41380-024-02811-2

Walsh BT et al. 1987. Hypothalamic-pituitary-adrenal-cortical activity in anorexia nervosa and bulimia. Psychoneuroendocrinology. 12(2):131–140. https://doi.org/10.1016/0306-4530(87)90043-6

Walsh K, Blalock DV, Mehler PS. 2020. Hematologic findings in a large sample of patients with anorexia nervosa and bulimia nervosa. Am J Hematol. 95(4):E98–e101. https://doi.org/10.1002/ajh.25732.

Walter C, Rottler E, von Wietersheim J, Cuntz U. 2015. QT-correction formulae and arrhythmogenic risk in female patients with anorexia nervosa. Int J Cardiol. 187:302–303. https://doi.org/10.1016/j.ijcard.2015.03.230

Walton E et al. 2022. Brain structure in acutely underweight and partially weight-restored individuals with anorexia nervosa: a coordinated analysis by the ENIGMA Eating Disorders Working Group. Biol Psychiatry. 92(9):730–738. https://doi.org/10.1016/j.biopsych.2022.04.022

Wanby P, Berglund J, Brudin L, Hedberg D, Carlsson M. 2016. Increased ferritin levels in patients with anorexia nervosa: impact of weight gain. Eat Weight Disord. 21(3):411–417. https://doi.org/10.1007/s40519-015-0246-4

Wang K et al. 2011. A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. Mol Psychiatry. 16(9):949–959. https://doi.org/10.1038/mp.2010.107

Watson HJ, Davies HL, Palmos AB. 2023. Genetics of eating disorders. In: Robinson P et al., editors. Eating disorders: an international comprehensive view. Springer International Publishing. p 1–25. https: https://doi.org/10.1007/978-3-030-97416-9_44-1

Watson HJ et al. 2022. Common genetic variation and age of onset of anorexia nervosa. Biol Psychiatry Glob Open Sci. 2(4):368–378. https://doi.org/10.1016/j.bpsgos.2021.09.001

Watson HJ et al. 2019. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet. 51(8):1207–1214. https://doi.org/10.1038/s41588-019-0439-2

Wentz E et al. 2021. Thirty years after anorexia nervosa onset, serum neurofilament light chain protein concentration indicates neuronal injury. Eur Child Adolesc Psychiatry. 30(12):1907–1915. https://doi.org/10.1007/s00787-020-01657-7.

Wesner K et al. 2023. Therapeutic reference range for olanzapine in Schizophrenia: systematic review on blood concentrations, clinical effects, and dopamine receptor occupancy. J Clin Psychiatry. 84(5). https://doi.org/10.4088/JCP.22r14626

Westwater ML et al. 2021. Dissociable hormonal profiles for psychopathology and stress in anorexia and bulimia nervosa. Psychol Med. 51(16):2814–2824. https://doi.org/10.1017/S0033291720001440

Westwater ML et al. 2022. Characterizing cerebral metabolite profiles in anorexia and bulimia nervosa and their associations with habitual behavior. Transl Psychiatry. 12(1):103. https://doi.org/10.1038/s41398-022-01872-7

Whitelaw M, Lee KJ, Gilbertson H, Sawyer SM. 2018. Predictors of complications in anorexia nervosa and atypical anorexia nervosa: degree of underweight or extent and recency of weight loss? J Adolesc Health. 63(6):717–723. https://doi.org/10.1016/j.jadohealth.2018.08.019

Wilcox H et al. 2024. The role of circadian rhythms and sleep in anorexia nervosa. JAMA Netw Open. 7(1):e2350358. https://doi.org/10.1001/jamanetworkopen.2023.50358

Wilson BC et al. 2023. An open-label pilot trial of faecal microbiome transfer to restore the gut microbiome in anorexia nervosa: protocol. BMJ Open. 13(7):e070616. https://doi.org/10.1136/bmjopen-2022-070616.

Winkler LA, Frølich JS, Schulpen M, Støving RK. 2017. Body composition and menstrual status in adults with a history of anorexia nervosa-at what fat percentage is the menstrual cycle restored? Int J Eat Disord. 50(4):370–377. https://doi.org/10.1002/eat.22600

Winston AP. 2012. The clinical biochemistry of anorexia nervosa. Ann Clin Biochem. 49(Pt 2):132–143. https://doi.org/10.1258/acb.2011.011185.

Woll S et al. 2025. Applying AI in the context of the association between device-based assessment of physical activity and mental health: systematic review. JMIR Mhealth Uhealth. 13:e59660. https://doi.org/10.2196/59660

Wolz I, Fagundo AB, Treasure J, Fernández-Aranda F. 2015. The processing of food stimuli in abnormal eating: a systematic review of electrophysiology. Eur Eat Disord Rev. 23(4):251–261. https://doi.org/10.1002/erv.2366

Workman C, Blalock DV, Mehler PS. 2020. Bone density status in a large population of patients with anorexia nervosa. Bone. 131:115161. https://doi.org/10.1016/j.bone.2019.115161

Wray NR et al. 2021. From basic science to clinical application of polygenic risk scores: a primer. JAMA Psychiatry. 78(1):101–109. https://doi.org/10.1001/jamapsychiatry.2020.3049

Wray NR et al. 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 50(5):668–681. https://doi.org/10.1038/s41588-018-0090-3.

Wronski M-L et al. 2024. Dynamic amygdala nuclei alterations in relation to weight status in anorexia nervosa are mediated by leptin. J Am Acad Child Adolesc Psychiatry. 63(6):624–639. https://doi.org/10.1016/j.jaac.2023.08.015

Wronski M-L et al. 2023a. Differential alterations of amygdala nuclei volumes in acutely ill patients with anorexia nervosa and their associations with leptin levels. Psychol Med. 53(13):6288–6303. https://doi.org/10.1017/S0033291722003609

Wronski M-L et al. 2025. Structural alterations of thalamic nuclei and their associations with leptin levels in patients with anorexia nervosa. Prog Neuropsychopharmacol Biol Psychiatry. 136:111248. https://doi.org/10.1016/j.pnpbp.2025.111248

Wronski ML et al. 2023b. Explicating the role of amygdala substructure alterations in the link between hypoleptinemia and rumination in anorexia nervosa. Acta Psychiatr Scand. 148(4):368–381. https://doi.org/10.1111/acps.13607

Wu YK et al. 2024. Peripheral biomarkers of anorexia nervosa: a meta-analysis. Nutrients. 16(13):2095. https://doi.org/10.3390/nu16132095

Xu C et al. 2025. C-reactive protein (CRP) levels in people with eating disorders: a systematic review and meta-analysis. J Psychiatr Res. 181:653–662. https://doi.org/10.1016/j.jpsychires.2024.12.039

Xu J et al. 2022. Plasma concentrations of short-chain fatty acids in active and recovered anorexia nervosa. Nutrients. 14(24):5247. https://doi.org/10.3390/nu14245247

Yan J, Wang A, Cao J, Chen L. 2020. Apelin/APJ system: an emerging therapeutic target for respiratory diseases. Cell Mol Life Sci. 77(15):2919–2930. https://doi.org/10.1007/s00018-020-03461-7

Yang QZ et al. 2011. The antidepressant-like effect of human opiorphin via opioid-dependent pathways in mice. Neurosci Lett. 489(2):131–135. https://doi.org/10.1016/j.neulet.2010.12.002

Yarlagadda A, Alfson E, Clayton AH. 2009. The blood brain barrier and the role of cytokines in neuropsychiatry. Psychiatry (Edgmont). 6(11):18–22.

Yasuhara D et al. 2005. Glucose tolerance predicts short-term refeeding outcome in females with anorexia nervosa. Psychosom Med. 67(4):669–676. https://doi.org/10.1097/01.psy.0000170332.47378.a1

Ye J, Qin Y, Wang D, Yang L, Yuan G. 2019. The relationship between circulating ANGPTL8/betatrophin concentrations and adult obesity: a meta-analysis. Dis Markers. 2019(1):5096860–5096867. https://doi.org/10.1155/2019/5096860

Yilmaz Z et al. 2023. Predicting eating disorder and anxiety symptoms using disorder-specific and transdiagnostic polygenic scores for anorexia nervosa and obsessive-compulsive disorder. Psychol Med. 53(7):3021–3035. / https://doi.org/10.1017/S0033291721005079

Yilmaz Z et al. 2017. Exploration of large, rare copy number variants associated with psychiatric and neurodevelopmental disorders in individuals with anorexia nervosa. Psychiatr Genet. 27(4):152–158. https://doi.org/10.1097/YPG.0000000000000172

Yu M, Yu B, Chen D. 2024. The effects of gut microbiota on appetite regulation and the underlying mechanisms. Gut

Microbes. 16(1):2414796. https://doi.org/10.1080/19490976.2024.2414796

Yücel B, Ozbey N, Polat A, Yager J. 2005. Weight fluctuations during early refeeding period in anorexia nervosa: case reports. Int J Eat Disord. 37(2):175–177. https://doi.org/10.1002/eat.20050

Žaja O, Fiolić M, Ćuk MC, Tiljak MK. 2021. "The role of L. reuteri DSM17938 in nutritional recovery and treatment of constipation in children and adolescents with anorexia nervosa - a randomized, double blind, placebo controlled study. Clin Nutr ESPEN. 46:47–53. https://doi.org/10.1016/j.clnesp.2021.08.016.

Zhang JV et al. 2005. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science. 310(5750):996–999. https://doi.org/10.1126/science.1117255

Zhang S et al. 2020. White matter abnormalities in anorexia nervosa: psychoradiologic evidence from meta-analysis of diffusion tensor imaging studies using tract based spatial statistics. Front Neurosci. 14:159. https://doi.org/10.3389/fnins.2020.00159

Zhang Y et al. 1994. Positional cloning of the mouse obese gene and its human homologue. Nature. 372(6505):425–432. https://doi.org/10.1038/372425a0.

Zhou C et al. 2018. Effect of selective serotonin reuptake inhibitors on bone mineral density: a systematic review and meta-analysis. Osteoporos Int. 29(6):1243–1251. https://doi.org/10.1007/s00198-018-4413-0.

Zierer C, Behrendt C, Lepach-Engelhardt AC. 2024. Digital biomarkers in depression: a systematic review and call for standardization and harmonization of feature engineering. J Affect Disord. 356:438–449. https://doi.org/10.1016/j.jad.2024.03.163

Zipfel S, Löwe B, Reas DL, Deter HC, Herzog W. 2000. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. Lancet. 355(9205):721–722. https://doi.org/10.1016/s0140-6736(99)05363-5