Unravelling sources of wellbeing and illbeing: The role of genetic, environmental, and social factors

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Submitted for the degree of PhD at the Department of Psychology, Faculty of Social Sciences, University of Oslo

2023

Series of dissertations submitted to the
Faculty of Social Sciences, University of Oslo
No. 1010

ISSN 1504-3991

Cover: UiO.
Print production: Graphic center, University of Oslo.

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Acknowledgements

This thesis, and the work that comprises it, is the result of contributions and support from many people. First, I wish to express my deep gratitude to my supervisors: Espen Røysamb, Ragnhild Bang Nes, and Eivind Ystrøm.

Thank you, Espen, for believing in me and supporting me from the beginning until the end of this journey. I have benefitted immensely from your experience, competence, and deep knowledge and understanding of both the subject matter and research methodology. Thank you for your openness and for allowing me to pursue my own ideas. I have deeply appreciated our many long conversations, also about other topics than research, as life unfolded itself when conducting this work.

Thank you, Ragnhild, for your support and contributions to this work. You have shaped my thinking about wellbeing and its measurement profoundly. Your energy and drive, for research and research communication both, are deeply inspiring to me and others in your proximity.

Thank you, Eivind, for welcoming me and believing in me from when I was a student and to today. For our many collaborations, our countless conversations about research and other topics, and for your invaluable support over the years. I continue to try to learn all that I can from you.

I would like to express my gratitude to my colleagues in research and the administration both at the PROMENTA Research Center and at the Department of Psychology at the University of Oslo. I also wish to acknowledge and thank the Research Council of Norway for funding this PhD and the participants who were part of all the studies.

Finally, I wish to thank my mother Cecilie Daae and my father Arild Bjørndal—my greatest sources of inspiration and support. This work is dedicated to you. I am blessed with a large family and thank all my siblings (Christian, Sander, Andrea, Ulrik, Ben) and their

partners and children (Ebbe and Lila), Meetali, Jonny, my grandparents, Farmor, and in loving memory of Farfar. Thank you to my dear friends, both at the University of Oslo and my friends from elsewhere. And to my Lisa: Thank you for your love, patience, and for our adventure.

Summary

The overarching aim of this thesis was to advance current understanding of genetic and environmental influences on multiple aspects of mental health, including wellbeing and symptoms of anxiety and depression (i.e., 'illbeing'). In particular, this thesis aimed to shed light on the role of social factors, which are conceptualised as key determinants of wellbeing and risk of mental disorders in several psychological theories, for mental health in adulthood. We applied multiple statistical methods and research designs to study the role of genetic, environmental, and social factors as potential sources of wellbeing and symptoms of common mental disorders (i.e., anxiety and depression) in adults.

More specifically, we examined the empirical structure of the wellbeing construct and its underlying genetic and environmental underpinnings, networks of environmental factors and mental health in the general population, associations between social factors and wellbeing when accounting for unmeasured familial confounding, and direct and indirect genetic effects (i.e., genetic effects of close family members mediated through the environment) on maternal depressive symptoms across the early childbearing years.

There are several conclusions which are drawn from the results of the studies comprising this thesis. First, the wellbeing construct empirically consists of multiple first-order wellbeing factors, which load on a higher-order wellbeing factor, and which show moderate genetic and substantial environmental influence. Social aspects may also be fundamental to the wellbeing construct itself. Second, key associations between environmental factors and mental health in the general population are between perceiving the social environment positively and better mental health and between having recently experienced discrimination and poorer mental health. Furthermore, many environmental characteristics show complex interrelationships and are jointly related to mental health. Third, diverse social factors remain robustly associated with wellbeing in adulthood when

accounting for unmeasured familial confounding. These social factors also show moderate genetic and substantial non-shared environmental influence. Fourth, indirect genetic effects from close family members, which operate through the environment, influence maternal depressive symptoms at several timepoints after birth. This highlights how genes and environments are intricately linked and the importance of intrafamilial influences on maternal depressive symptoms. Together, the findings accentuate the importance of social factors for multiple aspects of mental health in adulthood.

List of papers

This thesis is based on the following four papers:

Paper 1

Bjørndal, L. D., Nes, R. B., Czajkowski, N., & Røysamb E. (2023). The structure of wellbeing—a single underlying factor with genetic and environmental influences. *Quality of Life Research*, **32**, 2805-2816. https://doi.org/10.1007/s11136-023-03437-7

Paper 2

Bjørndal, L. D., Ebrahimi, O. V., Lan, X., Nes, R. B., & Røysamb, E. (2023). Mental health and environmental factors in adults: A population-based network analysis. *American Psychologist*. Advance online publication. https://doi.org/10.1037/amp0001208

Paper 3

Bjørndal L. D., Nes, R. B., Ayorech, Z., Vassend, O., & Røysamb, E. Multiple social factors are associated with wellbeing when accounting for shared genetic and environmental confounding. [Manuscript submitted for publication]. Department of Psychology, University of Oslo.

Paper 4

Bjørndal, L. D., Eilertsen, E. M., Ayorech, Z., Cheesman, R., Ahmadzadeh, Y. I., Baldwin, J. R., Ask, H., Hannigan, L. J., McAdams, T. A., Havdahl, A., Nes, R. B., Røysamb, E., & Ystrom, E. (in press). Disentangling direct and indirect genetic effects from partners and offspring on maternal depression using trio-GCTA. *Nature Mental Health*.

General Background

Mental disorders contribute strongly to the burden of disease worldwide, in particular depressive and anxiety disorders (GBD 2019 Diseases and Injuries Collaborators, 2020). Current treatment efforts are only to a minor extent reducing this burden (Holmes et al., 2018). In Norway, the lifetime prevalence of anxiety and depressive disorders is 25% and 20%, respectively, and a minority of affected individuals have been in contact with healthcare providers (Folkehelseinstituttet, 2018). Furthermore, some data indicate that the prevalence of anxiety and depressive symptoms has increased in young people since the 1990s (Krokstad et al., 2022). High prevalence and challenges related to treatment access and efficacy underline the importance of public health efforts which reduce the occurrence of mental disorders in the population.

An explicit aim for societies across the world is not only to reduce the burden of mental disorders but moreover to create opportunities and conditions for population thriving and wellbeing. This aligns with the acknowledgement that mental health reflects more than the absence of mental disorders and that wellbeing constitutes a key component of mental health (World Health Organization, 2004). The third UN Sustainable Development Goal (i.e., goals to which all member states of the UN adhere) focuses on ensuring healthy lives and wellbeing at all ages (United Nations General Assembly, 2015).

Developing and implementing effective interventions to improve population mental health, including both reducing the prevalence of mental disorders and increasing wellbeing, requires a comprehensive understanding of what impacts mental health. Disentangling aetiological influences, such as genetic and environmental effects, can potentially inform and improve both treatment and preventive efforts. Nevertheless, identifying the causes, risk, and protective factors affecting mental disorders has been called a ‘grand challenge’ of current

global mental health research and policy (Collins et al., 2011). Thus, more research is needed to better understand risk factors and causes of poor mental health outcomes.

Both conceptual models and findings from psychological research have underlined the critical importance of social variables for mental health and wellbeing. For instance, the biopsychosocial model provides an overall framework for understanding influences, including biological, psychological, and social variables, on health (Engel, 1977, 1980). This model emphasises aspects of the social context, at multiple levels, as key factors which affect mental health. Indeed, numerous social factors are associated with the occurrence of common mental disorders in the population, such as stressful interpersonal events (e.g., Kendler et al., 1999) and lower social support (Choi et al., 2023). Similarly, a range of social determinants are related to people's levels of experienced happiness (Helliwell & Aknin, 2018).

The overall aim of this thesis was to examine genetic and environmental influences on wellbeing and symptoms of mental disorders. Across four different studies, we applied different research designs and statistical approaches to advance current understanding of genetic and environmental factors and how these are related to multiple aspects of mental health. All studies incorporated an explicit focus on how social factors are tied to mental health in adulthood.

In this introduction, I first explain some basic concepts relevant for the interpretation of our findings and the broader literature. I then proceed to describe and discuss genetically informative designs, with an emphasis on twin studies and genome-wide complex trait analysis. Next, I describe the network approach to studying mental health and network analysis. Following this, I detail the aims and methods of the thesis and each individual paper. I proceed to discuss the findings of each study both in relation to each other and the broader body of literature each paper is situated in. I then describe several methodological

considerations necessary to be mindful of when interpreting the findings. Finally, I provide some recommendations for future studies in the field.

Basic Concepts

Wellbeing

Happiness has been a topic of philosophy for millennia and wellbeing notions from antiquity remain influential today (e.g., Waterman, 1990). Several prevailing theories in the wellbeing literature present distinct conceptualisations of the construct. One influential contemporary model is the 'Subjective Wellbeing' (SWB) model (Diener, 1984; Diener et al., 2018). The SWB model incorporates three key components: The presence of positive affect, absence of negative affect, and experienced satisfaction with life. The literature on SWB is vast and many empirical studies have established both important predictors of SWB and associated outcomes (Diener et al., 2018).

Life satisfaction constitutes an integral component of the SWB model (Diener, 1984; Diener et al., 2018). Specifically, this encompasses a person's cognitive evaluation of satisfaction with their own life. Thus, life satisfaction is predominantly related to an individual's experienced contentment with life, in contrast to the other two components of SWB which are primarily related to affect. While correlated with affective aspects of wellbeing, life satisfaction is distinguished both theoretically and empirically from these (Lucas et al., 1996). Evidence suggests that both personality traits and contextual factors like how one experiences specific domains of life contribute to evaluations regarding one's satisfaction with life (Pavot & Diener, 2008). The Satisfaction With Life Scale (SWLS) (Diener et al., 1985) is an extensively used measure of life satisfaction and was applied in multiple papers in this thesis.

Another widely studied model of wellbeing is the 'Psychological Wellbeing' (PWB) model (Ryff, 1989, 2014). Six components are central to the PWB framework: self-

acceptance, autonomy, personal growth, purpose in life, environmental mastery, and positive relationships. As for SWB, the PWB has spawned many inquiries into its predictors and related outcomes, such as health and longevity (Ryff, 2014). The SWB and PWB models are typically classified as hedonic (i.e., accentuating experienced pleasantness in life) and eudaimonic (i.e., accentuating experienced meaning in life), respectively (Gallagher et al., 2009).

Depressive Symptoms

Core symptoms of depression in the 5th version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) include depressed mood and/or lack of interest or pleasure in previously enjoyable activities, of which at least one is required for a major depressive disorder diagnosis (MDD; American Psychiatric Association, 2013). Depression and depressive symptoms can be assessed according to diagnostic manuals or using self-report measures. In research, depression diagnoses are typically assessed using clinical diagnostic interviews, such as the Composite International Diagnostic Interview (Robins et al., 1988).

Depressive symptoms are frequently measured using shorter scales in epidemiological studies. The papers in this thesis which examined possible influences on depressive symptoms were based on short-forms of a single measure of anxiety and depressive symptoms—The Hopkins Symptom Checklist (SCL: Hesbacher et al., 1980; Tambs & Røysamb, 2014). While a thorough discussion of this topic is beyond the scope of this thesis, variation in operationalization and measurement of depression across studies is an important challenge in psychological (e.g., Fried et al., 2022) and genetically informative research (Cai et al., 2020). As heterogeneous conceptualisations of depression across studies can have implications for study results (e.g., the genes underpinning a clinical depression diagnosis may not be the same as the genes associated with a broader depression phenotype), I will distinguish between

'depression', referring to diagnoses assessed using diagnostic interviews, and 'depressive symptoms', referring to symptoms measured using questionnaires.

Anxiety Symptoms

Anxiety comprises several different diagnoses, ranging from generalized anxiety disorder to specific phobias (American Psychiatric Association, 2013). Several symptoms, such as excessive worrying, are common across anxiety disorders. One paper (Paper 2) in this thesis probes relationships between environmental factors and symptoms of anxiety, in which anxiety symptoms were measured using a short-form of the SCL. As for depression, I will distinguish between 'anxiety' (i.e., anxiety diagnoses assessed with diagnostic interviews) and 'symptoms of anxiety' (i.e., symptoms measured with self-report questionnaires).

The Relationship Between Wellbeing and Illbeing

In this thesis, I use 'mental health' as a broad term which comprises both wellbeing and symptoms of mental disorders. This is in alignment with a definition of mental health which does not solely emphasise the absence of mental disorder but also the presence of wellbeing (World Health Organization, 2004). Previous research has conceived of the relationship between wellbeing and mental disorders in different ways. For instance, this has been conceptualised as a spectrum, ranging from 'flourishing' to 'mental disorder' (Huppert, 2005, 2009). Another theoretical model emphasises that wellbeing and mental disorder are related but distinguishable, with one dimension representing mental health (i.e., wellbeing) and the other presence (or absence) of mental disorder (Westerhof & Keyes, 2010). No studies in this thesis aimed to study the relationship between wellbeing and mental disorders specifically. However, together the findings shed light on mental health constructs—incorporating both measures of wellbeing and symptoms of mental disorders—and their associations with genetic and environmental factors.

Social Factors

Aspects of the social environment represent key influences on health, not only in humans, but across numerous species (Snyder-Mackler et al., 2020). Several influential theories in psychological research have emphasised the vital significance of social relations for mental health. For instance, Self-Determination Theory posits that humans have evolved to be fundamentally social creatures and that experiencing relatedness is a basic psychological need, mirroring other primary needs such as those which are physiological (Ryan & Deci, 2017). This need (together with the other basic psychological necessities) must be satisfied for people to experience wellbeing and good mental health. Other theories have emphasised the importance of similar social aspects such as belonging and interpersonal attachment (Baumeister & Leary, 1995), and also the potential role of other people in mitigating effects of stressful events on risk of mental disorders such as depression (Lakey & Cronin, 2008). In this thesis, I will use the term 'social factors' as a broad expression which subsumes both how an individual experiences one's social environment (e.g., perceived social support) and social aspects which could be conceived of as more trait-like (e.g., attachment).

Studying Genes and Environment in Wellbeing and Illbeing

Three papers in this thesis are based on genetically informative designs, including both quantitative genetic and genomic methods. I therefore describe core concepts of quantitative genetics and genomics in the subsequent section. These lines of research have yielded findings with important implications for current understanding of genetic and environmental influences on mental health. I give examples of key studies of each method applied to the study of wellbeing, anxiety, and depression, throughout.

Twin Studies and Quantitative Genetic Theory

The Logic of Twin Studies

Twin studies, which are based on examining the degree of similarity for one or more traits among individuals in twin pairs, have been conducted since the 1920s (Loehlin, 2022). Classical twin studies compare phenotypic similarity among monozygotic (MZ) and dizygotic (DZ) twins (Boomsma et al., 2002; Plomin et al., 2013). MZ co-twins share all their inherited genetic material, as they derive from one fertilized egg, whereas DZ co-twins share 50% of their segregating genes. If both twins in MZ and DZ pairs have grown up in the same family environment, any excess similarity among MZ co-twins compared with DZ co-twins for a given trait can be attributed to their higher genetic similarity. In other words, observing a higher correlation among MZ co-twins compared with DZ co-twins provides support for the role of genetic factors in explaining individual differences in the phenotype being studied.

The 'classical twin design' (CTD) compares correlations among MZ and DZ twins to infer the role of genetic and environmental factors (Boomsma et al., 2002). This design can be applied to examine the role of genetic and environmental influences on a single trait (univariate analyses) or across multiple traits (multivariate analyses). More recently, the CTD has been extended in various ways, such as to accommodate the inclusion of other types of relatives, repeated measurements across time, and even including the children of twins (Hagenbeek et al., 2023; Røysamb & Tambs, 2016).

Quantitative Genetic Theory and the Biometric Model

Twin and family studies are based on quantitative genetic theory. An influential way to model genetic and environmental effects on phenotypes is the biometrical approach (Eaves et al., 1978; Fisher, 1918; Jinks & Fulker, 1970). The biometric model explains variation in a phenotype by four potential factors: additive genetic effects, non-additive genetic effects, shared environmental effects, and non-shared environmental effects (Plomin et al., 2013).

These are typically referred to as 'A', 'D', 'C', and 'E' effects, respectively. A effects comprise the additive sum of individual effects of genes across the genome. D effects refer to interaction effects among genes across the genome. Such non-additive genetic effects can result from dominance (i.e., interaction effects at a given locus) and epistasis (i.e., interaction effects across loci). The effects of C comprise environmental influences which make twins (or other siblings) more similar. In contrast, E effects refer to environmental influences which reduce similarity among twins. This definition of non-shared environmental effects implies that the estimate of E also captures random measurement error.

MZ and DZ twins are correlated differently for genetic effects, which allows for the decomposition of variation in phenotypes into the contributions of each component of the biometric model, when data from both types of twins (or other family members) are available (Plomin et al., 2013). MZ twins share all additive and non-additive genetic influences—as they share all their genetic material—meaning that MZ twins are correlated 1.0 for A and D effects. A effects are correlated .5 and non-additive dominance effects .25 for DZ twins. The effects of shared environmental factors contribute to similarity among twins and are therefore perfectly correlated for both MZ and DZ twins. The effects of the non-shared environment contribute to dissimilarity and are therefore uncorrelated among both types of twins.

The decomposition of observed variance in the trait being studied into the components of the biometric model is often conducted using structural equation modelling (SEM) or other advanced statistical approaches. These methods typically compare the fit of models derived from genetic theory to observed data to estimate the effects of genes and environment. However, estimates of these effects can also be inferred from comparing twin correlations (Boomsma et al., 2002; Plomin et al., 2013). An estimate of 'narrow heritability', i.e., the influence of A, is given by doubling the difference in observed correlations between MZ and DZ twins for the phenotype (i.e., $2 * (r_{MZ} - r_{DZ})$). An estimate of C is given by subtracting

the heritability h^2 from the observed correlation for MZ twins (i.e., $r_{MZ} - h^2$). An estimate of E is given by subtracting the correlation among MZ twins from 1 (i.e., $1 - r_{MZ}$). The CTD cannot usually decompose observed variance into all four components (i.e., A, D, C, and E effects) unless other types of relatives are included, and thus, often requires assuming that genetic effects are either additive or non-additive in model fitting (Røysamb & Tambs, 2016).

The *heritability* of a trait describes the proportion of individual differences in a given trait which is explained by genetic variation (Boomsma et al., 2002; Plomin et al., 2013). As previously noted, an estimate of so-called 'narrow heritability' includes only A effects, whereas an estimate of 'broad heritability' includes both A and D effects. The heritability statistic is subject to several important limitations and must be carefully interpreted (Plomin et al., 2013). Importantly, heritability is a population statistic which describes the extent to which variation in a trait in a group of people is explained by genetic variation. It is dependent on the particular sample, context, and measurement of phenotypes, in a given study.

Twin Studies Have Shown That all Traits are Heritable—But Only Partially

A 2015 meta-analysis summarizing 50 years of twin studies of more than 17,800 phenotypes concluded that this line of research has shown that all human traits are at least partially heritable (Polderman et al., 2015). This is in agreement with what Plomin et al. (2016) highlighted as the number one replicated finding in the field of behaviour genetics (all psychological traits show considerable genetic influence), and the 'three laws of behavioural genetics' (Turkheimer, 2000).

The second finding highlighted by Plomin et al. (2016) concerns the environment: as no traits are 100% heritable, this provides clear evidence for the importance of environmental factors in explaining individual differences in complex traits. Most of these environmental effects are not shared between siblings and therefore reflect the non-shared component of the biometric model (Plomin, 2011; Plomin & Daniels, 1987). Importantly, environmental

influences in the biometric model are defined with respect to the effects they have on similarity among family members. Non-shared environmental factors may therefore comprise both unique experiences for siblings and experiences common to siblings but which affect them differently (Turkheimer, 2000). Furthermore, many non-shared environmental influences are likely to be largely unsystematic and related to chance (Smith, 2011).

Genetic and Environmental Effects on Wellbeing, Anxiety, and Depression

Twin and family-based studies have provided important insights into genetic and environmental influences on wellbeing, anxiety, and depression. Estimates of the heritability of wellbeing generally lie between 30% and 40% (Bartels, 2015; Nes & Røysamb, 2015). Nes & Røysamb (2015) found that the best-fitting model across 15 samples included the effects of A and E only. However, several well-powered extended twin designs have reported significant non-additive effects (Bartels, 2015). In sum, findings from previous studies have shown that the heritability of wellbeing is moderate and that the majority of individual differences in wellbeing are accounted for by non-shared environmental factors.

Anxiety disorders have a heritability comparable to that of wellbeing with estimates across studies around 30% to 50% (Hettema et al., 2001; Polderman et al., 2015; Shimada-Sugimoto et al., 2015). Heritability estimates for depressive diagnoses are close to estimates for anxiety with most studies showing that the residual variance in depression risk is primarily explained by non-shared environmental effects (Pettersson et al., 2019; Sullivan et al., 2000). The heritability of recent symptoms of depression and anxiety may be slightly lower, e.g., estimated at 25% in one large Norwegian sample (Czajkowski et al., 2010). Heritability of the risk of receiving a depression diagnosis within a given year is lower when compared with the heritability of depression risk across the lifespan (Bjørndal et al., 2022).

Genetic and environmental factors can contribute to stability and change in traits across time. There is moderate stability in both symptoms of anxiety and depression

symptoms across development from adolescence to adulthood which is largely accounted for by genetic factors (Waszczuk et al., 2016). For symptoms of anxiety and depression, twin studies have also pointed to the influence of genetic innovation across early development, i.e., when new genetic factors which influence a trait come into play across time, and genetic attenuation, i.e., when the influence of previously important genetic factors diminishes (Kendler et al., 2008; Waszczuk et al., 2016). Genetic innovation seems to occur less in adulthood for symptoms of anxiety and depression compared with earlier in development (Nes et al., 2007; Nivard et al., 2015). As for symptoms of anxiety and depression in adulthood, the stability of subjective wellbeing in adulthood is mostly due to stable genetic factors, whereas change is mostly related to non-shared environmental influences (Lykken & Tellegen, 1996; Nes et al., 2006; Røysamb, Nes, et al., 2014).

Co-Twin Control Designs

Confounding in Observational Studies

Studies which seek to identify risk factors for poor mental health are usually not, for ethical or other reasons, possible to conduct using randomized controlled trials (RCTs; Rohrer, 2018). Observational studies are required for this purpose but are often limited by the potential influence of unmeasured confounding, i.e., when unmeasured variable(s) influence both the risk factor and the outcome. This means that detecting the causal influence of an exposure on an outcome based on observational data is challenging, as associations may (partly or fully) reflect the influence of confounding variables.

One such possible confounder is genetic factors. As previously mentioned, all human traits, including aspects of mental health, are partially heritable (Polderman et al., 2015). Many supposedly ‘environmental’ measures, such as stressful life events and social support, also show moderate genetic influence (Kendler & Baker, 2007). Genetic predisposition can therefore act as a confounder in many studies of environmental factors and mental health. For

instance, an observed positive association between social support and wellbeing, whereby perceiving one's partner as more supportive is associated with higher levels of wellbeing, could be explained by genetic factors which predispose people to *both* experiencing partners as more supportive and higher wellbeing in their lives in general (e.g., a positivity orientation). This can introduce a correlation between social support and wellbeing which reflects their common genetic underpinnings and not the effect of experiencing social support on wellbeing. This kind of confounding has been called 'the bane of observational data' in epidemiology (Rohrer, 2018).

Comparing Discordant Twin Pairs: The Co-Twin Control Design

Genetic data can be useful for diminishing the risk of confounding in observational studies and can therefore be leveraged to bolster causal inference (Pingault et al., 2018). Hence, data with MZ and DZ twins can be useful for purposes beyond the mere quantification of the extent to which genetic and environmental effects explain variation in traits. An individual twin in an MZ twin pair represents a perfect match for their co-twin in terms of genes and shared environment, as MZ twins are correlated at unity for these influences. In co-twin control designs, a twin who has been exposed to a risk factor can be compared with their non-exposed twin for a given outcome, so that twins serve as their co-twins' 'controls' (McAdams et al., 2020). A counterfactual framework of causality represents a useful way of understanding the logic of co-twin control designs (Pingault et al., 2018). In this scenario, a person is both exposed and not exposed to a given risk factor. The effect of exposure is determined by any difference in outcome between exposure and non-exposure. Such a scenario (which is impossible in practice) is approximated by the co-twin control design, as non-exposed twins serve as the match for their exposed co-twin. In RCTs, the control group can be understood as the counterfactual to the treatment group if random assignment has ensured that confounders are equally distributed across both groups (van Dijk et al., 2022).

The co-twin control design aims to approximate such a scenario since twins will share many unmeasured (familial) confounders.

An example of a co-twin control design could be to investigate happiness among twin pairs discordant for partner relationship satisfaction, i.e., twin pairs in which one twin is satisfied with their relationship and the other is not. By modelling the association between twin pair differences (with respect to relationship satisfaction) and wellbeing, the resulting associations control for potential confounding by A and C (McGue et al., 2010). Confounding by these factors is fully adjusted for in estimates for MZ twins, which are correlated at unity for genetic effects, and partially in estimates for DZ twins, as DZ twins are correlated .5 for A. If associations are of similar magnitude in the full sample and within discordant MZ and DZ twins, this is indicative of absence of confounding by genetics or shared environmental effects. If the association is not observed within twin pairs, this suggests that the relationship is fully explained by confounding. Attenuation of associations within twin pairs is indicative of partial confounding. Co-twin control analyses can be conducted within a linear mixed model regression framework (Carlin et al., 2005).

Co-Twin Control Studies of Wellbeing, Anxiety, and Depression

There are several examples of co-twin control studies of wellbeing, anxiety, and depression, which have yielded insights into influences on these aspects of mental health. For instance, bereavement following the loss of a spouse has been associated with lower levels of life satisfaction within twin pairs for women (Liechtenstein et al., 1996). One longitudinal co-twin control study did not find evidence of lower back pain on future development of anxiety and depressive symptoms, but that associations were explained by shared familial confounding (Fernandez et al., 2017). On the contrary, associations between stressful life experiences and major depression likely at least in part reflect causal influence of exposure to such events on depression risk (Bjørndal et al., 2022; Kendler et al., 1999). Thus, the co-twin

control design has been applied to examine associations between exposure to multiple factors and mental health, while adjusting for unmeasured familial confounding.

Co-Twin Control Designs: A Note of Caution

Co-twin control studies have often been interpreted as confirming causal links between exposure to risk factors and outcomes (McAdams et al., 2020). While co-twin control designs (and other sibling designs) account for confounders which are shared between twins (i.e., genetic and shared environmental factors), this design is unable to adjust for unmeasured confounding and associations can also be biased by measurement error (Frisell et al., 2012; Sjölander et al., 2022). Both factors threaten the validity of such designs. Confounders which are not shared within families can result in more biased associations in sibling comparison studies. Measurement error can result in more attenuated effects in such studies compared with studies of non-sibling samples. Nevertheless, co-twin control designs represent one useful tool in epidemiological studies. As such, this design, and other sibling designs, can be integrated within a triangulation approach (Lawlor et al., 2016) to strengthen causal inference in epidemiology.

Genotype-Environment Interaction and Correlation

Twin studies have also yielded insights into interactions between genes and environment with respect to their influence on traits, including wellbeing and symptoms of anxiety and depression. Genotype-environment interaction (GxE) effects occur when genetic influences are contingent on environmental factors or when environmental influences are contingent on genotypes (Hagenbeek et al., 2023; Plomin et al., 1977). Such interaction can also be interpreted as moderator effects of either genetic or environmental factors on the impact of genes or environment. For instance, one previous study found that the heritability of subjective wellbeing is lower among married people compared with non-married people, which is indicative of an interaction effect between genetic influences on wellbeing and

relationships status (Nes, Røysamb, et al., 2010). It has also been found that the effect of stressful life events exacerbating risk of depression is higher in individuals with higher genetic risk (Kendler, Kessler, et al., 1995). Thus, twin and family-based studies can also shed light on interactive effects between genetic and environmental factors—and not only the main effects of each.

Genotype-environment correlation (rGE) occurs when exposure to environments correlates with genotype (Hagenbeek et al., 2023; Plomin et al., 1977). Such correlations can arise from multiple processes, including passive (i.e., associations between inherited genotypes and rearing environments), evocative (i.e., associations between genetically influenced phenotypes and the reactions of other people to the given phenotypes), and active (i.e., associations between genotypes and the selection of environments by people) processes (Jaffee & Price, 2008; Plomin et al., 1977). For instance, rGE was implicated in one previous twin study in which genetic influences on wellbeing-related traits which influence behaviour were correlated with genetic effects on positive life events (Wootton et al., 2017). rGE for symptoms of anxiety and depression in children has also recently been examined using genomic data (e.g., Cheesman et al., 2020).

The Genomic Revolution and GWAS

Advances in genome sequencing and mapping led to the development and application of novel genetically informative methods in the late 1990s and early 2000s (Psychiatric GWAS Consortium Coordinating Committee, 2009; Visscher et al., 2012). Candidate gene studies and genome-wide association (GWAS) studies both leverage measured genotype data to investigate associations between genetic variants and complex traits. Candidate gene studies, which examine associations between specific genes and traits, have not yielded robust findings for major depression (Border et al., 2019), anxiety disorders (Shimada-Sugimoto et al., 2015), nor wellbeing (van de Weijer et al., 2022).

The aim of GWAS studies is to identify single nucleotide polymorphisms (SNPs) associated with traits across the genome. SNPs tag common variation in the human genome: The SNPs measured on genotype chips are typically restricted to those occurring in the population above a certain threshold (Visscher et al., 2012). GWAS studies have now identified a number of genetic variants associated with depression phenotypes (Howard et al., 2019; Levey et al., 2021; Wray et al., 2018), anxiety phenotypes (Levey et al., 2020; Otowa et al., 2016; Purves et al., 2020), and wellbeing (Baselmans & Bartels, 2018; Jamshidi et al., 2020; Okbay et al., 2016). For instance, Baselmans & Bartels (2018) identified SNPs associated with both hedonic and eudaimonic wellbeing, as well as high genetic correlation (i.e., genetic overlap) across the two phenotypes. Thus, recent GWAS studies have begun to yield insights into the architecture of genetic influences on these complex traits based on variation in measured DNA sequences in the population.

An important challenge in the field of genomics has been that of 'missing heritability'—the discrepancy in observed heritability estimates from quantitative genetic studies (such as twin designs) and genomic designs (such as GWAS; Manolio et al., 2009). For instance, the SNP-based heritability estimate for major depression has been reported at 8.7% (Wray et al., 2018), while, as previously noted, estimates from twin and family studies range between 30% and 40% (Pettersson et al., 2019; Sullivan et al., 2000). A thorough discussion of potential causes of such missing heritability is beyond the scope of this thesis. Nevertheless, a proposed remedy for this issue has been the advent of genome-wide complex trait analysis (GCTA) (Yang et al., 2010), which I will discuss in the subsequent section.

GCTA and Trio-GCTA

GCTA estimates the heritability of a trait based on measured SNPs across the genome (Yang et al., 2010, 2011, 2017). Thus, GCTA aims to estimate the heritability of complex traits based on genomic data but the goal is not to identify specific genetic variants associated

with the phenotypes. The statistical approach underlying GCTA is based on a mixed linear model approach and is now known as genomic relatedness matrix (GRM) restricted maximum likelihood (GREML) (Yang et al., 2017).

The GRM is a matrix which denotes the genetic relatedness estimated between pairs of individuals (based on SNP data) in a sample. GCTA has typically been used in samples of unrelated individuals. In large samples of non-related people, there is variation in the degree of relatedness between pairs of individuals due to chance, which can be leveraged to estimate the influence of narrow heritability on a phenotype (Eaves et al., 2014). Table 1 provides an example of a small GRM for four people, in which the values in the columns reflect their genetic relatedness coefficients.

Table 1.

Example Genomic Relatedness Matrix for Four Unrelated Individuals.

	Individual 1	Individual 2	Individual 3	Individual 4
Individual 1	1.00	.05	.03	.06
Individual 2	.05	1.00	.04	.07
Individual 3	.03	.04	1.00	.02
Individual 4	.06	.07	.02	1.00

Table 1 shows that some individuals have higher genetic similarity than others, e.g., individuals 1 and 4 have a higher genetic relatedness coefficient than individuals 1 and 3. This (chance) genetic relatedness among unrelated individuals (in a familial sense) and the phenotypic similarity among individuals for the trait being studied serves as the basis for estimating the heritability of the phenotype. Following the estimation of the GRM, GCTA then estimates variance components for additive genetic effects and the residual error using restricted maximum likelihood (Yang et al., 2017). The GRM is included as a random effect

in the mixed linear model and thus accounts for genetic similarity among individuals in the given sample.

A small number of studies have reported SNP-based heritability estimates for depression and depressive symptoms based on GCTA ranging from 21% to 32% (Laurin et al., 2015; Lee et al., 2013; Lubke et al., 2012). The SNP-based heritability for having had any anxiety disorder diagnosis across was estimated to 14% in one previous study (Otowa et al., 2016). Another previous GCTA study estimated the heritability of SWB (measured using single items) to between 5% and 10% when measurement error was unaccounted for (Rietveld et al., 2013).

Extending GCTA to Trio-GCTA

GCTA was extended to account for maternal influences on child traits by Eaves et al. (2014). Subsequently, this method was extended to quantify direct genetic effects and indirect genetic effects from close family members based on data from genotyped parent-offspring trios (Eilertsen et al., 2021). Direct genetic effects refer to the effects of inherited genetic variants on a phenotype, whereas indirect genetic effects represent genetic effects which influence a person's trait but are dependent on the genes of other individuals (Kong et al., 2018; McAdam et al., 2014; Young et al., 2019). Such indirect genetic effects could arise when inherited genetic variants influence risk for a trait, such as depression, both in the index person (i.e., the person who inherited the alleles) and also influence another person's depression risk.

Indirect genetic effects are mediated by the environment and highlight a form of genotype-environment correlation. For instance, it has been shown that 'genetic nurture' effects, whereby genetically influenced parent behaviours affect traits in children, occur for educational attainment (Kong et al., 2018), depressive symptoms (Cheesman et al., 2020), and some ADHD symptoms (Eilertsen et al., 2022). While most GWAS studies aim to identify

genetic variants with causal influence on phenotypes, the findings of typical GWAS studies can also reflect such indirect genetic effects (Young et al., 2019). Hence, examining direct and indirect genetic effects can advance the understanding of genetic and environmental effects on traits and may also have implications for the identification of phenotype-associated individual genetic variants.

A Note on the Structure of Wellbeing and its Influences

The structure of the wellbeing construct, i.e., its fundamental constituents, remains a topic of debate in the literature. More recent models have accentuated other aspects of the wellbeing construct compared with the SWB and PWB models described previously, such as social wellbeing (Keyes, 1998), and/or integrated components across theoretical models (Forgeard et al., 2011; Seligman, 2018). A comprehensive operationalisation of the wellbeing construct is necessary for its measurement. Appropriate measurement of wellbeing has implications for researchers and policymakers alike (Diener & Seligman, 2004; Ruggeri et al., 2020).

Adequate measurement has been argued to require the conceptualisation of wellbeing as multidimensional, going beyond the theoretical distinction between hedonic and eudaimonic models (Ruggeri et al., 2020). As previously noted, genetically informative studies of wellbeing have yielded insights into its genetic and environmental effects. For instance, several studies have investigated influences on wellbeing using multivariate analyses (Bartels, 2015), which can provide insights into genetic and environmental factors which explain covariation between interrelated traits (Plomin et al., 2013). However, these studies have often examined wellbeing components within one theoretical framework, such as the SWB (Bartels & Boomsma, 2009) or the PWB (Gigantesco et al., 2011). Less is known about genetic and environmental effects on and across broader notions of wellbeing which encompass multiple theoretical frameworks.

A Note on Latent Variable Models and Structural Equation Modelling

Many of the approaches discussed thus far implicitly or explicitly study latent variables. To provide context for my subsequent discussion of network theory and analysis, I briefly elaborate on the use of latent variables in factor analysis and twin studies.

Factor analytic models are based on the assumption that there are underlying unobserved, i.e., latent, variables which explain variation in observed items (Bollen, 2002; Watkins, 2020). For instance, the items of a wellbeing scale are often assumed to reflect the effects of the underlying latent construct of wellbeing on the observed items. The latent construct (wellbeing, in this case) therefore reflects a common cause of observed covariation among the items (Schmittmann et al., 2013). Assuming that all observed items reflect an underlying latent construct is also implied when the items of a symptom measure of a mental disorder (e.g., depression) are summed and a threshold value is applied to distinguish between individuals who have or do not have the disorder (Fried & Nesse, 2015).

In many genetically informative studies, such as applications of the CTD, quantitative genetic theory is used to formulate theoretical models (often in the form of variance-covariance matrices) which are then compared against observed data using SEM (Plomin et al., 2013). By applying an iterative model optimization process, the parameter values which result in the best approximation to the observed variance-covariance matrix are estimated (e.g., using maximum likelihood). As these studies do not rely on measured genotype data, they quantify the influence of latent genetic and environmental factors on trait(s). Thus, in twin studies, it is often the influence of latent genetic and environmental factors on latent outcomes which is quantified.

Network Theory and Analysis

The network approach provides an alternative perspective on the study of mental health compared with traditional latent variable models. In Paper 2, we apply network

analysis to investigate associations between environmental factors and population mental health. I therefore describe key concepts related to network theory and analysis in the following section.

Network Theory

Network theories posit that mental disorders, such as depression, result from the interactions between symptoms, which can be represented using a network structure (Borsboom, 2017). Such theories specify the relevant components of the network, their interactions, and generate predictions (Borsboom et al., 2022). Borsboom (2017) describes four basic principles of a network theory of mental disorders. First, mental disorders can be represented as complex structures with interacting constituents (the principle of 'complexity'). Second, individual symptoms assessed in diagnostic systems and symptom measures match the elements of the network (the principle of 'symptom-component correspondence'). Third, the structure of the network arises through the causal influence of symptoms on one another (the principle of 'direct causal connections'). Fourth, some symptoms group together and are more strongly linked than others—therefore particular constellations of symptoms manifest more often in conjunction (e.g., depressive symptoms). One implication of these four principles is that factors which influence one symptom can have effects across a network through symptom-level connections. Another implication is that comorbidity between mental disorders arises through connections between symptoms of different disorders—comorbidity is therefore 'an intrinsic feature of mental disorders' (Borsboom, 2017, p. 7). This understanding of psychopathology networks consisting of symptoms with mutual causal influence is in alignment with the conceptualisation of mental disorders as 'mechanistic property cluster kinds' (Kendler et al., 2011).

Importantly, the network approach can be contrasted to common cause theories of mental disorders. In the latter, the latent construct of a mental disorder is thought to cause the

symptoms of the disorder (Borsboom & Cramer, 2013; Schmittmann et al., 2013). For instance, depression is assumed to be the cause of symptoms such as fatigue, irritability, and feelings of hopelessness. The strong correlation between these symptoms is assumed to result from the influence of the common cause (depression); removal of the common cause (e.g., by treatment) would be assumed to remove the correlation between the symptoms. While this approach has been widely applied in medicine, few common pathogenic pathways for mental disorders have been established (Borsboom, 2017; Kendler et al., 2011). Network theory, on the contrary, is predicated on the assumption that symptoms have causal influence on each other. Mental disorders as phenomena are assumed to emerge through such symptom interactions. This emphasis on interactions within systems consisting of multiple symptoms also highlights that the network perspective can be understood as a system-based approach (Borsboom et al., 2022; Bringmann et al., 2023). There are few formal network theories applied to specific mental health constructs to date but notable examples include a recently proposed computational model of panic disorder (Robinaugh et al., 2019) and a model of resilience (Lunansky et al., 2023).

Network Analysis

Network analysis represents statistical methods which focus on identifying the important elements of networks and their interconnections (Borsboom et al., 2021; Borsboom & Cramer, 2013). In the last two decades, applications of network analysis to studying mental health have gained popularity and become widespread (Robinaugh et al., 2020).

A network model represents the multivariate probability distribution for the variables in a dataset as a network (Borsboom et al., 2022). Individual elements (i.e., variables) in the network are typically referred to as ‘nodes’ and their estimated interrelationships as ‘edges’. The joint probability distribution is commonly represented using the pairwise Markov random field (PMRF) graphical model, in which the conditional associations between all variables in

a dataset is estimated (Borsboom et al., 2021; Epskamp et al., 2022). The association between nodes A and B can be interpreted as the two being associated when controlling for all other variables in the network model (i.e., conditional on all other variables). Following network estimation, a network model is often visualized using network plots and the topology of the network described using multiple statistics. One such frequently used category of statistics comprise measures of node centrality, which aim to be indicative of the importance of nodes in a network by quantifying their strength of connections to other nodes in the same network (Bringmann et al., 2019).

Different network analysis models can accommodate data measured at different levels. A model which can be applied when all variables are continuous is the Gaussian graphical model (Borsboom et al., 2021). Mixed graphical models (MGMs) can accommodate both binary and continuous variables (Haslbeck & Waldorp, 2020). Model selection is performed to choose the network model which maximises the probability of including 'true positive' edges (i.e., edges present in the data generating model) and excluding 'true negative' edges (i.e., edges not present in the data generating model; Blanken et al., 2022). This also typically involves statistical regularization, whereby some edges are estimated to be zero due to a penalization on the associations, which results in a sparser network and excludes (likely) spurious edges.

An important part of network analyses is to conduct additional investigations of characteristics of the estimated network model, such as inspecting its accuracy and robustness (Borsboom et al., 2021; Epskamp et al., 2018). This is necessary because the parameters estimated in network models, as is the case for statistical estimation more generally, is affected by sampling variation (Fried, Epskamp, et al., 2022). Bootstrapping approaches (i.e., randomly selecting data with replacement and re-estimating statistics) are widely used for examining network accuracy and robustness, for instance by generating bootstrapped

confidence intervals for estimated edge weights and examining the stability of node centrality measures across subsamples of the data.

Network studies have yielded novel insights into both the structure of mental disorders and mental health and associations with risk factors. For instance, in a sample of psychiatric patients, Beard et al. (2016) found that sad mood and worry were particularly strongly connected to other nodes, providing insights into symptom-level connections for anxiety and depression. Network analysis has also been applied to examine the structure of wellbeing in light of more recently proposed models (e.g., Heshmati et al., 2022). Finally, network studies have identified associations between mental health and external risk factors, such as between psychotic symptoms and childhood trauma (Isvoranu et al., 2017), and wellbeing and individual and environmental characteristics (McElroy et al., 2021).

Aims of the Thesis

The main aims of this thesis were to: (1) Advance current understanding of genetic and environmental effects on wellbeing and illbeing (i.e., symptoms of anxiety and depression); and (2) investigate the importance of social factors for mental health in adulthood. We used multiple genetically informative designs and statistical approaches to examine these overarching research questions. I describe the specific objectives of each individual paper in brief below.

Paper 1: The Structure of Wellbeing: A Single Underlying Factor With Genetic and Environmental Influences

In Paper 1, we sought to investigate the structure of wellbeing empirically across three large independent samples of adults and the underlying genetic and environmental underpinnings of wellbeing factors. The structure of wellbeing is a continuing topic of debate. Few studies have estimated genetic and environmental effects on general wellbeing components.

Paper 2: Mental Health and Environmental Factors in Adults: A Population-Based Network Analysis

In Paper 2, we had three aims. First, to identify the most important nodes and edges in networks with overall mental health constructs (wellbeing and symptoms of anxiety and depression) and environmental characteristics. Second, to examine more granular associations between environmental factors and specific wellbeing aspects, anxiety symptoms, and depressive symptoms. Third, to assess the replicability of our analyses in an independent sample. Few previous studies have examined how multiple environmental factors are associated with each other and jointly with population mental health using a network analysis approach.

Paper 3: Multiple Social Factors are Associated With Wellbeing When Accounting for Shared Genetic and Environmental Confounding

In Paper 3, we aimed to estimate genetic and environmental effects on and across multiple social factors using multivariate Cholesky models, and to examine associations between these social factors and wellbeing in adulthood accounting for unmeasured familial confounding. Few previous studies have examined genetic and environmental influences on social factors. The majority of previous observational studies which have identified links between social factors and wellbeing have not accounted for possible confounding by shared genetic and/or environmental factors.

Paper 4: Disentangling Direct and Indirect Genetic Effects From Partners and Offspring on Maternal Depression Using Trio-GCTA

In Paper 4, our aim was to quantify direct genetic effects and indirect genetic effects of partners and offspring on maternal depressive symptoms across early childhood using trio-GCTA. Few previous studies have examined indirect genetic effects on maternal depressive symptoms.

Materials and Methods

Samples, Procedures, and Measures

Multiple samples were used in the papers comprising this thesis. I therefore describe the samples, procedures, and measures administered in each study separately.

Paper 1: The Structure of Wellbeing: A Single Underlying Factor With Genetic and Environmental Influences

Paper 1 was based on three separate samples. The full sample size across all analyses was 21,529 in total.

Sample 1: Quality of Life Survey 2020.

The Quality of Life Survey 2020 (QoL 2020) was conducted by Statistics Norway between March 9th and March 29th 2020 (Pettersen & Støren, 2020). A random sample of 40,000 adults was drawn from the Norwegian population. The response rate was 43.6%, yielding a total sample size of 17,423 individuals (6 individuals were subsequently excluded by Statistics Norway for data privacy reasons).

While a representative sample was drawn from the Norwegian population, the final sample was characterised by overrepresentation of individuals with certain demographic characteristics due to attrition (Pettersen & Støren, 2020). Respondents with higher education level, in the age group 45-66 years, and with Norwegian country background were overrepresented.

Sample 2: Quality of Life Survey in Hallingdal 2019.

The Quality of Life Survey in Hallingdal 2019 (QoL 2019) was conducted by Statistics Norway between April 1st and April 14th 2019 (Støren & Todorovic, 2019). A random sample of 4,000 individuals was drawn stratified by the population size within the six municipalities of Hallingdal in Norway. The response rate was 53%, yielding a final sample size of 2,125. Respondents in the age group 45-55 years and with higher education were

overrepresented in the sample. The demographic characteristics in the QoL 2019, QoL 2020, and Quality of Life Survey 2021 (QoL 2021) samples are reported in Table 2.

Table 2.

Demographic Characteristics in the QoL 2019 (N = 2,125), QoL 2020 (N = 17,417), and QoL 2021 (N = 17,487) samples.

Characteristics	QoL 2019 Number of respondents (%)	QoL 2020 Number of respondents (%)	QoL 2021 Number of respondents (%)
Gender			
Female	1126 (53.0)	8914 (51.2)	9038 (51.7)
Male	995 (46.8)	8430 (48.4)	8360 (47.8)
Other	3 (.1)	68 (.4)	75 (.4)
Age group			
18-24	194 (9.1)	1798 (10.3)	1607 (9.2)
25-44	609 (28.7)	5443 (31.3)	5418 (31.0)
45-64	888 (41.8)	6637 (38.1)	6761 (38.7)
65-74	318 (15.0)	2499 (14.3)	2606 (14.9)
75 and older	116 (5.5)	1040 (6.0)	1095 (6.3)
Education level			
Unknown or no education	65 (3.1)	481 (2.8)	409 (2.3)
No higher education	1395 (65.6)	9619 (55.2)	9163 (52.4)
Higher education	665 (31.3)	7317 (42.0)	7915 (45.3)

Sample 3: The Norwegian Twin Registry 1945-1960 Cohort.

We used data collected in 2016 from a cohort of twins born between 1945 and 1960 in the Norwegian Twin Registry (NTR; T. S. Nilsen et al., 2016). The response rate was 64%, yielding a total sample size of 1,987 individuals. Zygosity was determined by the use of a questionnaire. Data were collected from 708 complete twin pairs (i.e., twin pairs in which both twins participated) of the same sex and 571 single responders. This included responses from 528 female MZ twins, 627 female DZ twins, 375 male MZ twins, and 457 male DZ twins.

Measures.

Our analyses were based on 37 wellbeing items administered in the QoL 2020 survey. These originated from multiple scales: the SWLS (Diener et al., 1985), The Warwick-Edinburgh Mental Well-being Scale (WEMWBS: Tennant et al., 2007), The Mastery Scale (Pearlin & Schooler, 1978), and the Flourishing Scale (Diener et al., 2009). Ten items which have been recommended for monitoring of quality of life in the Norwegian population (Nes et al., 2018) were included, as well as three items from the European Social Survey (ESS; European Social Survey, 2013), and five items adapted from OECD (2013). All items used in analyses conducted for Paper 1 are reported in Appendix A.

We used the same items in the analyses conducted with the QoL 2019 data as described for the QoL 2020 data, with one exception. One item assessing how happy individuals think they will be with their life in five years was only included in the QoL 2020 survey.

We used multiple items which were administered in all three samples. Some items were also unique to the 2016 data collection in the NTR 1945-1960 Cohort. We used items from the SWLS (Diener et al., 1985), OECD (2013), Revised Life Orientation Test (LOT-R; Scheier et al., 1994), Symptom Checklist-8 (SCL-8; Tambs & Røysamb, 2014), Differential Emotions Scale (DES; Izard et al., 1993), General Self-Efficacy Scale (GSE; Leganger et al., 2000; Tambs & Røysamb, 2014), and the Relationship Satisfaction Scale (RSS; Røysamb, Vittersø, et al., 2014) in the analyses conducted with data from this cohort. The wellbeing scales which were administered in each sample are reported in Table 3.

Table 3.

Measures Used Across Each Sample in Study 1.

QoL 2019	QoL 2020	NTR 1945-1960 Cohort
SWLS[a]	SWLS[a]	SWLS[a]
WEMWBS[b]	WEMWBS[b]	OECD (2013)
The Mastery Scale	The Mastery Scale	LOT-R[d]
Flourishing scale	Flourishing scale	SCL-8[e]
ESS[c]	ESS[c]	DES[f]
OECD (2013)	OECD (2013)	GSE[g]
Nes et al. (2018)	Nes et al. (2018)	RSS[h]

Notes. [a]Satisfaction with Life Scale; [b]Warwick-Edinburgh Mental Well-being Scale; [c]European Social Survey; [d]Revised Life Orientation Test; [e]Symptom Checklist-8; [f]Differential Emotions Scale; [g]General Self-Efficacy Scale; [h]Relationship Satisfaction Scale.

Paper 2: Mental Health and Environmental Factors in Adults: A Population-Based Network Analysis

Paper 2 was based on two separate samples with the full sample size across analyses > 31,000.

Sample 1: Quality of Life Survey 2021.

QoL 2021 was conducted by Statistics Norway between March 8th and March 28th 2021 (Pettersen & Støren, 2021). A representative and random sample of 40,000 adults was drawn from the general population in Norway. The response rate was 43.7%, yielding a total sample size of 17,493 individuals. 6 individuals were subsequently excluded by Statistics Norway for data privacy reasons. There was some overrepresentation in this sample by individuals with similar characteristics as in QoL 2020.

Sample 2: Quality of Life Survey 2020.

The data from QoL 2020 were used for the purpose for replicating our main analyses. The QoL 2020 sample and procedures have been described for Paper 1 and are therefore not described further here.

Measures.

Wellbeing was measured using the SWLS (Diener et al., 1985) and symptoms of anxiety and depressive symptoms with a short-form of the SCL (Hesbacher et al., 1980; Tambs & Røysamb, 2014). Furthermore, 14 environmental characteristics were evaluated using self-report items, all of which have been proposed for assessing quality of life in the Norwegian population (Nes et al., 2018). The environmental characteristics included housing satisfaction and perceptions of issues in the living environment (e.g., problems with noise or contamination), perceptions of the residential area (e.g., safety, problems with crime or violence, hiking and play areas in close proximity), perceptions of the social environment, experiences of recent discrimination, and perceptions of societal institutions (e.g., trust in the public, influence on government). Two environmental characteristics based on registry data, household crowding and living in an urban or rural area, were also included. Identical items were used in the analyses conducted in both samples. All SWLS, SCL items, and environmental characteristics are reported in Appendix B.

Paper 3: Multiple Social Factors are Associated With Wellbeing When Accounting for Shared Genetic and Environmental Confounding

The Norwegian Twin Registry 1945-1960 Cohort.

We used data from the same cohort of twins in the NTR described for Paper 1. We used data collected in 2016 and 2021. The mean age at the 2016 wave of data collection was 63 years (*SD* = 4.5). Characteristics of the data collected in 2016 have been previously described for Paper 1.

The 2021 data collection wave had a response rate of 35%. We only used data from individuals who participated in both 2021 and 2016, which comprised 1,228 individuals in total. Of these, 335 were female MZ twins, 371 female DZ twins, 236 male MZ twins, and

286 male DZ twins. The mean age at the 2021 wave of data collection was 68.5 years (*SD* = 4.4).

Measures.

Wellbeing was measured using the SWLS. Several social factors were also included in the analyses. Satisfaction with the partner relationship was measured using the RSS, which includes five items and response options on a 6-point scale ranging from 'Strongly disagree' to 'Strongly agree' (Røysamb et al., 2014). Disruptions in social relationships were assessed based on the reporting of three stressful experiences of interpersonal nature: divorce, separation, or termination of cohabitation; conflicts in the partner relationship; and conflicts with family, friends or neighbours. A composite variable was created with 1 indicating having experienced any of these events and 0 no events. Two dimensions of attachment (anxiety and avoidance) were measured using the Experiences in Close Relationship Scale (ECR-N12), which comprised 12 items and response options on a 7-point scale spanning 'Strongly disagree' (1) to 'Strongly agree' (7) (Olssøn et al., 2010). Loneliness was measured using a short-form of the UCLA Loneliness Scale comprising three items with response options on a 5-point scale from "Never" (1) to "Always" (5) (Hughes et al., 2004). Trust was measured using items adapted from the ESS, for which response options were on a 10-point scale from 0 to 10 (OECD, 2017). All items and their response formats are reported in Appendix C.

Paper 4: Disentangling Direct and Indirect Genetic Effects From Partners and Offspring on Maternal Depression Using Trio-GCTA

The Norwegian Mother, Father and Child Cohort Study.

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based study conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). All pregnant women in Norway were eligible to participate in MoBa at its beginning. Invitations to participate were sent to 277,702 women and the response rate was 41%. The MoBa cohort

comprises 114,500 children, 95,200 mothers, and 75,200 fathers in total. There is substantial attrition in MoBa across the measurement timepoints, described in closer detail in Magnus et al. (2016). We used data from version 12 of the quality-assured MoBa data files.

The sample comprised complete mother-partner-offspring trios and the quality control of genotype data retained 25,332 such trios. Subsequent data exclusions and final sample sizes are reported in the description of the statistical analyses for Paper 4.

Measures.

We used measures of maternal depressive symptoms administered at five measurement timepoints after birth. Depressive symptoms were measured using the four depressive symptoms of the SCL-8 (Hesbacher et al., 1980; Tambs & Røysamb, 2014). We also used genomic data from mothers, partners, and offspring. The genotype pipeline for MoBa is described in Corfield et al. (2022).

Statistical Analyses

The statistical analyses for Papers 1, 2, and 3 were conducted in the R Statistical Environment (R Core Team, 2022). Analyses for Paper 4 were conducted using the Julia programming language (Bezanson et al., 2017).

Paper 1: The Structure of Wellbeing: A Single Underlying Factor With Genetic and Environmental Influences

Our analysis strategy in Paper 1 consisted of three steps: (1) Examine the structure of wellbeing in QoL 2020 using exploratory factor analysis (EFA); (2) investigate the fit of the factor model identified in the EFA in an independent sample (QoL 2019) and the fit of a broadly similar model in another independent sample (the NTR 1945-1960 cohort) using confirmatory factor analysis (CFA); (3) estimate genetic and environmental influences on wellbeing factors in the NTR 1945-1960 cohort. The analysis code for Paper 1 is included in

the Supplementary Materials to the published paper and is available here: https://doi.org/10.1007/s11136-023-03437-7

Exploratory Factor Analysis.

EFA is based on the assumption that correlations between observed variables can be explained by a (smaller) number of latent variables (Bollen, 2002). The aim in EFA is to identify factors which explain as much common variation between observed items as possible. The loading of each observed item to its corresponding factor (i.e., the strength of influence of a factor on an observed item) and communality (i.e., proportion of variance in each item explained by the factors) are both estimated (Mair, 2018). The so-called 'fundamental equation' in factor analysis can be expressed as:

$$P = \Lambda\phi\Lambda' + \psi \quad (1)$$

In Equation (1), P represents the $m * m$ correlation matrix implied by the model (in which m is the observed items), Λ a matrix containing the factor loadings, ψ a $m * m$ matrix with unique factor variances, and ϕ represents the factor correlation matrix (Mair, 2018). This equation therefore conveys that the observed correlation matrix can be expressed as a function of the factor loading matrix, the factor correlation matrix, and a portion explained by unique factors. Loadings and communalities can be estimated with different approaches, including maximum likelihood, with the number of factors fixed before conducting the analysis.

We carried out EFA in accordance with recently published recommendations (Watkins, 2020). We used three criteria for identifying factors. We first examined a scree plot of eigenvalues (which gauge the amount of variance explained by each factor) to identify the 'break', after which extracting additional factors primarily explained error variance. We then conducted parallel analysis (i.e., a comparison of observed and simulated eigenvalues), keeping factors for which observed eigenvalues exceeded simulated eigenvalues. Third, we

applied the Minimum Average Partial (MAP) method. In MAP, partial correlation matrices are repeatedly estimated after extracting principal components. The average partial correlation is at its lowest when the common variance is removed, i.e., when the correct number of factors has been extracted.

The response formats of the items were on an ordinal level and we therefore used the weighted least squares solution for estimating and extracting factors. We subsequently applied oblique promax factor rotation allowing for correlation between the factors. We retained and rotated factors with other methods in sensitivity analyses. Missing data were handled using pairwise deletion, i.e., only unobserved values of individual variables were discarded. Following the extraction of factors, we conducted a new EFA based on the correlation matrix containing the factor intercorrelations, i.e., a hierarchical EFA (Watkins, 2020).

Confirmatory Factor Analysis.

Following the EFA, we examined the fit of the identified model in an independent sample using CFA. In CFA, factors and loading patterns are specified prior to conducting the analyses (Bollen, 2002). CFA and EFA otherwise correspond closely as they are mathematically based on the same fundamental equation (Mair, 2018). The diagonally weighted least squares estimator was applied, since this performs better than ML when data are at an ordinal level (Li, 2016). Missing data were handled with listwise deletion (i.e., participants were excluded if they had missing data for any of the items in the analysis).

Four indices were used to determine the model fit: The Comparative Fit Index, the Tucker-Lewis Index, the Root Mean Square Error of Approximation (RMSEA), and the Standardised Root Mean Square Residual. These measures reflect how well the relationships among the items in the observed data correspond to the relationships implied by the model (Watkins, 2020). The threshold values used to indicate good model fit were determined by commonly used conventions in the literature (Hu & Bentler, 1999).

Two CFAs were conducted for Paper 1. The first examined the fit of an identical model to the one identified in the EFA in an independent sample (QoL 2019), with the omission of one item as previously described. We proceeded to examine the fit of a broadly similar model with multiple first-order factors and a higher-order factor in the NTR 1945-1960 Cohort, as this study included partially different items. The latter CFA applied the same estimator, fit indices, and threshold values for determining model fit.

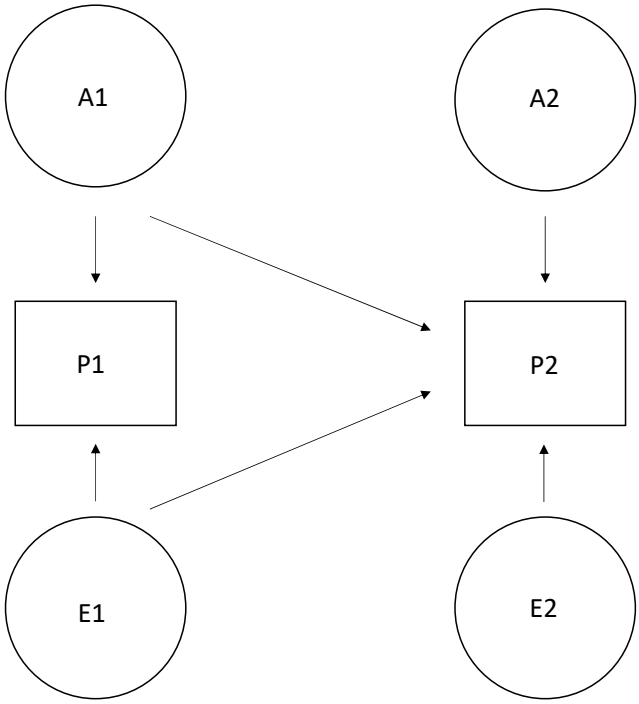
Multivariate Cholesky and Common Pathway Models.

We estimated genetic and environmental effects on wellbeing factors using multivariate twin models, which represent an extension of factor analysis to the case of genetically informative data (Neale & Maes, 2004; Plomin et al., 2013). Factors are specified for A, C (or D), and E effects, and statistics based on the twin data (means, variances, and covariances) allow for estimating the loadings of phenotypes on these factors, using maximum likelihood. Hence, such models aim to identify the best-fitting model, i.e., the model for which the model implied variance-covariance matrix for MZ and DZ twins (in the context of a twin study) most closely matches the observed variance-covariance matrix.

We first estimated multivariate Cholesky models (Loehlin, 1996; Neale & Maes, 2004). These models allow for estimating genetic and environmental influences on multiple traits and the extent to which such effects are overlapping across traits (i.e., genetic and environmental correlations). The Cholesky model specifies latent genetic and environmental factors equal to the number of traits studied, with the first factor explaining variance in all observed phenotypes. The second factor is uncorrelated with the first factor, thus explaining residual variance (this logic extends to additional factors if there are more traits being studied). A Cholesky model estimating A and E effects for two observed phenotypes is depicted in Figure 1.

Figure 1.

AE Cholesky Model with Two Phenotypes.



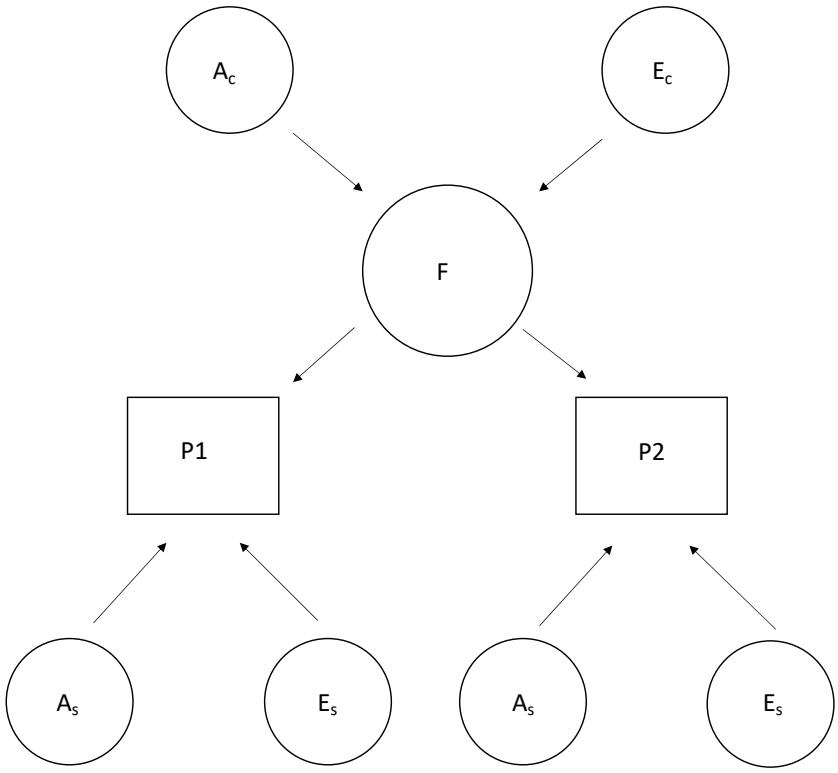
Notes. P1 refers to 'phenotype 1' and P2 refers to 'phenotype 2'.

Each participant received an index score (i.e., a sum score) in accordance with each wellbeing factor specified in the CFA. Multiple Cholesky models (models with ADE, ACE, AE, CE, and E effects, respectively) were compared in terms of model fit. We then estimated a Common Pathway (CP) model. The CP model posits that covariation between phenotypes is explained by a latent factor (Neale & Maes, 2004). The implication here would be that the covariation between the wellbeing index scores is explained by a common phenotypic wellbeing factor. This underlying phenotypic factor is influenced by genetic and environmental effects which are estimated. Factor loadings for the observed variables to the latent factor are also estimated and allow for examining the extent to which genetic and environmental influences on the latent factor manifest in the observed variables. Finally,

unique (i.e., residual) genetic and environmental effects on each trait are estimated. A CP model estimating A and E effects for two observed phenotypes is depicted in Figure 2.

Figure 2.

AE Common Pathway Model with Two Phenotypes.



Notes. P1 refers to 'phenotype 1' and P2 refers to 'phenotype 2'. 'F' refers to the common factor.

Model fit comparisons were based on RMSEA and the Akaike Information Criterion (AIC; Akaike, 1987). The AIC is the sum of minus two multiplied with the log-likelihood and double the number of estimated parameters, with lower values indicative of better model fit. Data were residualised on sex and age prior to the twin analyses to account for the influence of these covariates. The Cholesky and CP models were estimated with the *umx* (Bates et al., 2019) and *OpenMx* packages (Neale et al., 2016), which allow for model estimation using full-information likelihood (FIML). FIML uses all available data in the estimation of model parameters.

Paper 2: Mental Health and Environmental Factors in Adults: A Population-Based Network Analysis

The analysis code for Paper 2 is available in a public repository on the Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/PN7JE

Data Preparation and Topological Overlap.

We transformed the numeric variables using nonparanormal transformation (Jiang et al., 2021), which can be done to tackle skew in observed variables prior to network estimation (Blanken et al., 2022). The variables included in the network models were specified a priori. We therefore investigated potential topological overlap between nodes with a method which compares correlations for pairs of nodes to identify variables which exhibit very similar correlations (Jones, 2022). If the proportion of comparable correlations is above a threshold, including both nodes in the model is considered redundant. We examined topological overlap with the minimum zero-order correlation set to .5 and .25 and the threshold value for the proportion of significantly different correlations set to .25.

Mixed Graphical Models.

We estimated undirected networks using MGMs as our data consisted of both binary and numeric nodes. MGMs estimate the parameters of the PMRF through conducting a series of univariate statistical models and the conditional distribution of the nodes included in the PMRF with a generalized linear model (Epskamp et al., 2022). Appropriate link functions are specified depending on the measurement level of each individual node and the estimated parameters are then combined into one single network structure. This allows for modelling the joint distribution of variables of mixed type. As for several other network models, MGMs are commonly estimated using regularization which results in a sparser network (Blanken et al., 2022). Model selection was conducted based on the extended Bayesian information criterion.

The γ hyperparameter, which determines the penalization of edge weights, was set to the recommended value of .25 (Haslbeck & Waldorp, 2020).

The network was plotted and inspected using the Fruchterman-Reingold algorithm, a force-directed layout algorithm which plots nodes with stronger connections in closer proximity (Epskamp et al., 2012). We also estimated the predictability of each node, i.e., the extent to which each node is predicted by the other nodes included in the network (Haslbeck & Waldorp, 2018). The overall strength of connections between each node and all other nodes in the network was examined using strength centrality, which was calculated by taking the sum of all edge weights (in absolute values) for each node. We visualized the centrality estimates with radar plots, which has been proposed in previous studies (Ebrahimi et al., 2021).

All networks included gender, age, and sexual orientation to adjust for the influences of these covariates on the estimated associations. We also investigated the influence of several socioeconomic status (SES) variables on the associations in sensitivity analyses. These SES variables included registry-based household income, household debt, education level, and self-reported current employment. Participants who had missing data for any variables included in the network estimation were excluded prior to conducting analyses. This resulted in 1,869 exclusions for the overall mental health networks and 1,874 for the item-level networks.

Stability and Accuracy Analyses.

The stability of the strength centrality estimates was inspected using case-dropping bootstrapping. This generates an estimate of the correlation stability coefficient, which reflects the maximum number of observations which can be removed to maintain a correlation of .7 or higher with the original centrality indices with a certainty of 95% (Epskamp et al., 2018). Network accuracy was examined using nonparametric bootstrapping, which computes

bootstrapped 95% confidence intervals for edge weights. 1,000 samples were used in all bootstrapping analyses.

Replication of Networks.

Following the previously described network estimation, we estimated identical networks in an independent sample to assess the replicability of the networks across samples. Replicability was determined by inspecting the correlations between edge weights estimated in the main and replication samples and between strength centrality estimates in the main and replication samples.

Paper 3: Multiple Social Factors are Associated With Wellbeing When Accounting for Shared Genetic and Environmental Confounding

In Paper 3, we examined genetic and environmental effects on social factors and associations between social factors and wellbeing accounting for unmeasured familial confounding. The analysis code for Paper 3 is available in a public repository on OSF: https://osf.io/u69dy/?view_only=559618fcc7b4485999c74a288b13f87a

Multivariate Cholesky Models.

The Cholesky model has been described previously and is therefore not elaborated on further. We examined genetic and environmental effects on and across six social factors: relationship satisfaction, attachment anxiety, attachment avoidance, loneliness, disruptions in social relationships, and trust. We compared model fit of multivariate Cholesky models with ACE, AE, and E effects, based on AIC values. Missing data were treated using FIML, as previously described for Paper 1.

Co-Twin Control Analyses.

The logic of the co-twin control design has been described previously and is therefore not elaborated on further. Multilevel models were applied to conduct co-twin control analyses, modelling both within-family and between-family estimates simultaneously

(McAdams et al., 2020). The models included a random intercept on the twin pair level to account for the dependence in the data which reflected its twin structure, which also captures variability in the outcome due to within-pair factors. The models also included multiple fixed effects (i.e., effects which do not vary across the twin pair clusters): the twin pair mean score for each social factor, which represented the between-pair effect; each twin's individual score subtracted from the twin pair mean, which represented the within-pair effect; and sex and age (as covariates). The regression model with between- and within-pair effects is expressed in Equation (2), where x_{ij} represents a given social factor for twin *j* in twin pair *i*, and $\bar{x}_i$ represents the mean level of the social factor in twin pair *i* (Carlin et al., 2005):

$$y_{ij} = \beta_0 + \beta_W(x_{ij} - \bar{x}_i) + \beta_B\bar{x}_i + \varepsilon_{ij} \quad (2)$$

The within-pair effect (which represents the effect of differential exposure to the social factor on the outcome) is captured by the regression coefficient β_W and the between-pair effect is captured by β_B in Equation (2). The outcomes and predictors were standardized except for the disruptions in social relationships variable, as this was binary (with 1 indicating that the individual had experienced disruptions in social relationships). We examined the effects of disruptions in social relationships in the past year and disruptions having occurred at any time previously separately in the co-twin control analyses (in the Cholesky models, we assessed having experienced any disruptions at any timepoint previously).

We required that participants had responded to all items to be included in the analyses. We only analysed data from twin pairs in which both twins had responded to all items (i.e., complete twin pairs). Sample sizes ranged from 1,509 – 1,899 for concurrent wellbeing in the full sample; 438 – 656 for concurrent wellbeing in MZ twins; 978 – 1,191 for wellbeing measured six years later in the full sample; and 244 – 356 for wellbeing measured six years later in MZ twins.

Paper 4: Disentangling Direct and Indirect Genetic Effects From Partners and Offspring on Maternal Depression Using Trio-GCTA

In Paper 4, we applied trio-GCTA to quantify direct genetic effects and indirect genetic effects of partners and offspring on maternal depressive symptoms at five timepoints after birth: 6 months, 1.5 years, 3 years, 5 years, and 8 years.

Measure of Maternal Depressive Symptoms.

As previously noted, depressive symptoms were assessed using SCL-8. Mothers received sum scores for the four depressive symptoms in SCL-8 per timepoint. We applied a logarithmic transformation to reduce skewness in this variable for each timepoint. We subsequently standardised each symptom score using the mean score and standard deviation estimated for the first timepoint.

Genomic Relatedness Matrix.

We estimated a GRM which included the empirical estimates of genetic relatedness in our sample. To limit confounding of parameter estimates based on the inclusion of (closely) related individuals (which would have much higher genetic relatedness than two non-related people), a correlation of .10 between two individuals was specified as the threshold for the highest allowed genetic correlation (except for among pairs of parents and offspring). The number of parent-offspring trios used in analyses at each timepoint was 21,146 at 6 months, 17,789 at 1.5 years, 13,888 at 3 years, 10,360 at 5 years, and 10,582 at 8 years.

Trio-GCTA.

As previously noted, Eilertsen et al. (2021) extended GCTA to utilise genotyped data from mothers, partners, and offspring, to separate direct and indirect genetic effects on traits of the given family member being studied (i.e., the mother, partner, or child). This model allows for decomposing phenotypic variance into variance components which represent direct and indirect genetic effects on the phenotype, expressed in Equation (3):

$$Var(y_k) = \sigma_m^2 + \sigma_p^2 + \sigma_o^2 + \sigma_{om} + \sigma_{op} + \sigma_{mp} + \sigma_e^2 \quad (3)$$

The interpretation of the parameters in Equation (3) depends on which person is the focal individual in the study, i.e., if a phenotype of the mother, partner, or child, is being investigated (Eilertsen et al., 2021). If the focal individual is the mother, then σ_m^2 quantifies the variance explained by direct genetic effects, σ_p^2 the variance explained by indirect genetic effects from the partner, and σ_o^2 indirect genetic effects from the offspring. σ_{om} quantifies the covariance between direct genetic effects and offspring indirect genetic effects and σ_{op} the covariance between the offspring and partner indirect genetic effects. The parameter σ_{mp} quantifies the covariance between direct genetic effects and partner indirect genetic effects. Finally, σ_e^2 quantifies the residual variance of the phenotype, i.e., the proportion of variance not explained by the other variance components, which includes the effects of the non-shared environment.

We tested 5 models for each timepoint. The first model estimated all variance components and covariance parameters in Equation (3). The second model omitted the indirect genetic effects from offspring parameter (σ_o^2) and the covariance parameter for the direct effects and offspring indirect effect (σ_{om}). The third model omitted the indirect genetic effects from partners parameter (σ_p^2) and the covariance parameter for the direct effects and partner indirect effect (σ_{mp}). The fourth model omitted both covariance parameters for the direct effects and indirect effects from offspring and partners (σ_{om} and σ_{mp}). The final model estimated only direct genetic effects and the residual variance parameter (i.e., no indirect effects or covariances). The best-fitting model was selected for each timepoint based on the AIC. We also conducted likelihood ratio tests, comparing the goodness of fit of the full model (i.e., with all parameters estimated) and each individually nested model.

Ethics

All participants provided their informed consent to participate in the studies. The studies conducted by Statistics Norway (QoL 2019, QoL 2020, QoL 2021) were approved by Statistics Norway's data protection officer. These data were applied for and accessed via 'Sikt' (Norwegian Agency for Shared Services in Education and Research). The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The present MoBa study was approved by the Regional Committees for Medical and Health Research Ethics (project number: 2013/863). The MoBa data were accessed and analysed using the Services for sensitive data (TSD) at the University of Oslo, which provides a secure environment for collecting, storing, and analysing sensitive research data. The data collections conducted in the NTR 1945-1960 cohort were approved by the Regional Committees for Medical and Health Research Ethics (project numbers: 2015/958 and 2021/27872). These data were stored at a secure storage service at the University of Oslo. Thus, we ensured that all data were stored securely and analysed in appropriate software environments.

Main Findings

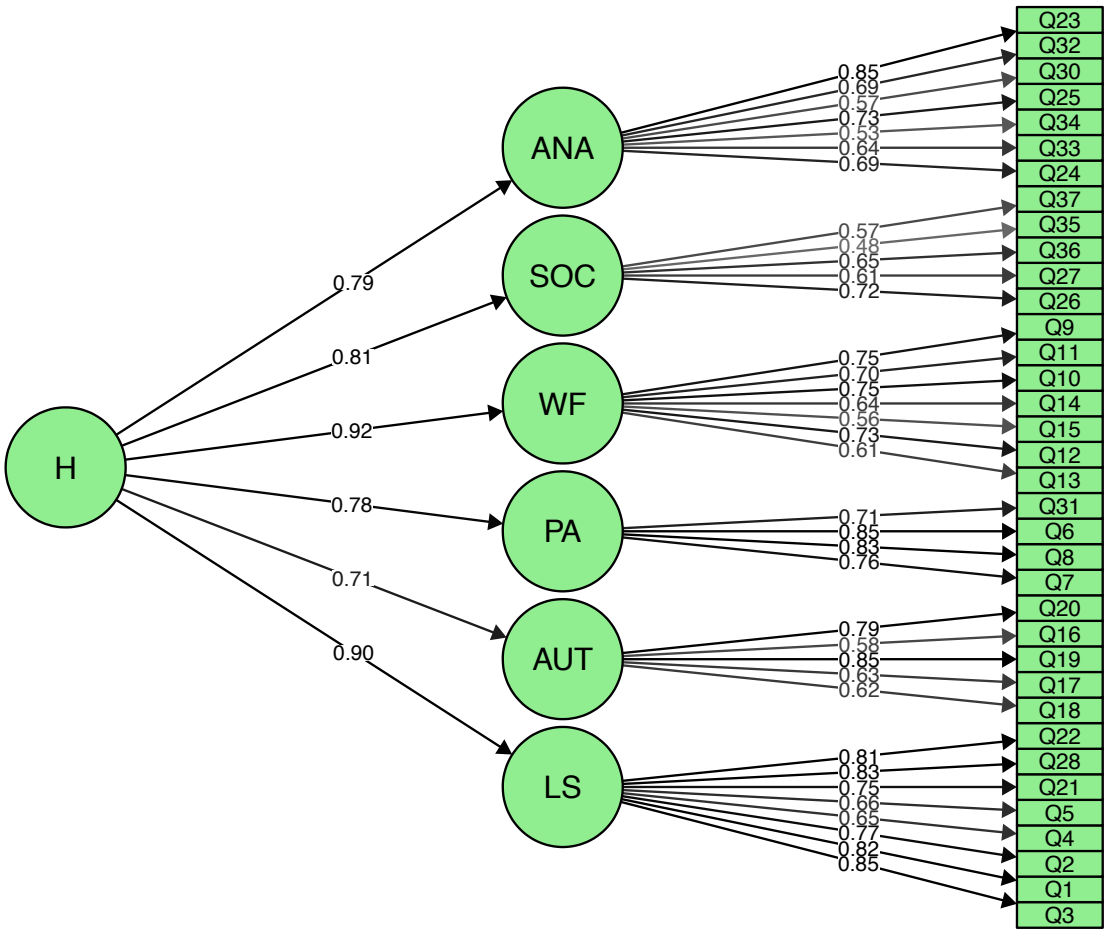
Paper 1: The Structure of Wellbeing: A Single Underlying Factor With Genetic and Environmental Influences

In Paper 1, we examined the structure of wellbeing across three independent samples using EFA and CFA and the genetic and environmental underpinnings of wellbeing factors. We identified a wellbeing structure with six components, all loading on a higher-order wellbeing factor. These six wellbeing components were interpreted as reflecting the constructs 'absence of negative affect', 'social, 'well-functioning', 'positive activation', 'autonomy', and 'life satisfaction'. The model identified using EFA had excellent fit in an independent sample. All wellbeing factors showed moderate genetic and substantial non-shared environmental influence, with heritability estimates for the first-order factors ranging

from 26% to 36%. The heritability of the latent phenotypic wellbeing factor in the CP model was 40%. Figure 1 displays the factor model and the loadings estimated in the CFA conducted in the QoL 2019 sample.

Figure 1.

CFA Results of Model With six First-Order Factors and one Higher-Order Factor.



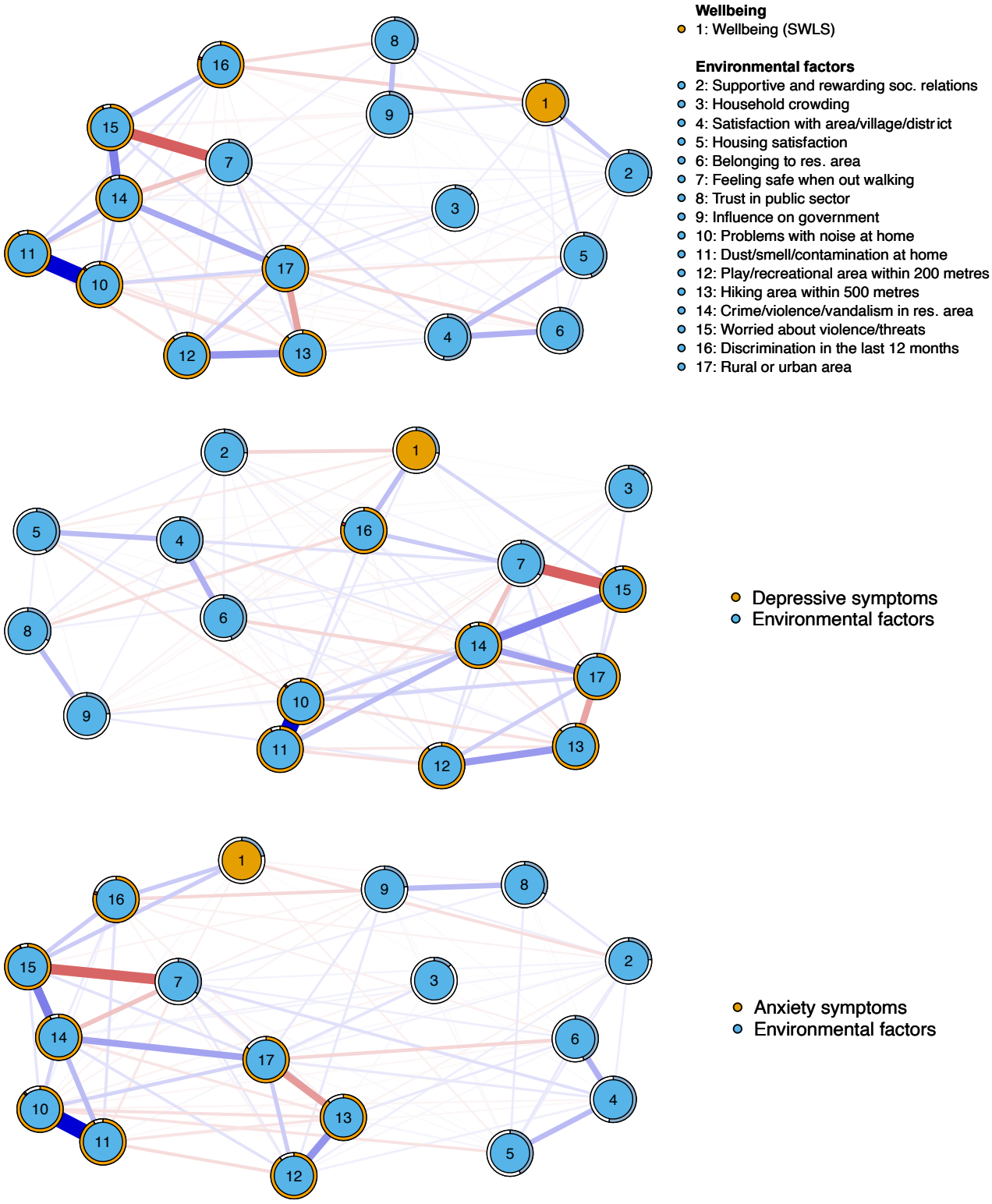
Notes. 'ANA' refers to absence of negative affect; 'SOC' refers to social; 'WF' refers to well-functioning; 'PA' refers to positive activation; 'AUT' refers to autonomy; and 'LS' refers to life satisfaction.

Paper 2: Mental Health and Environmental Factors in Adults: A Population-Based Network Analysis

In Paper 2, we examined associations between environmental factors and population mental health using network analysis. Key associations were observed between perceiving the social environment as supportive and better mental health and having recently experienced discrimination and poorer mental health. Several environmental characteristics were also strongly interrelated. The most strongly connected nodes comprised environmental factors. The predictability (i.e., proportions of explained variance) in the mental health nodes ranged from 22% (for anxiety symptoms) to 37% (for wellbeing). Further analyses suggested that edge weights had high accuracy and that centrality estimates exhibited high stability. The replicability of the associations and centrality estimates in an independent sample was very high, indicative of robustness of the results across samples. Figure 2 displays the networks estimated with environmental characteristics and overall mental health constructs.

Figure 2.

Networks With Overall Mental Health Nodes and Environmental Characteristics.

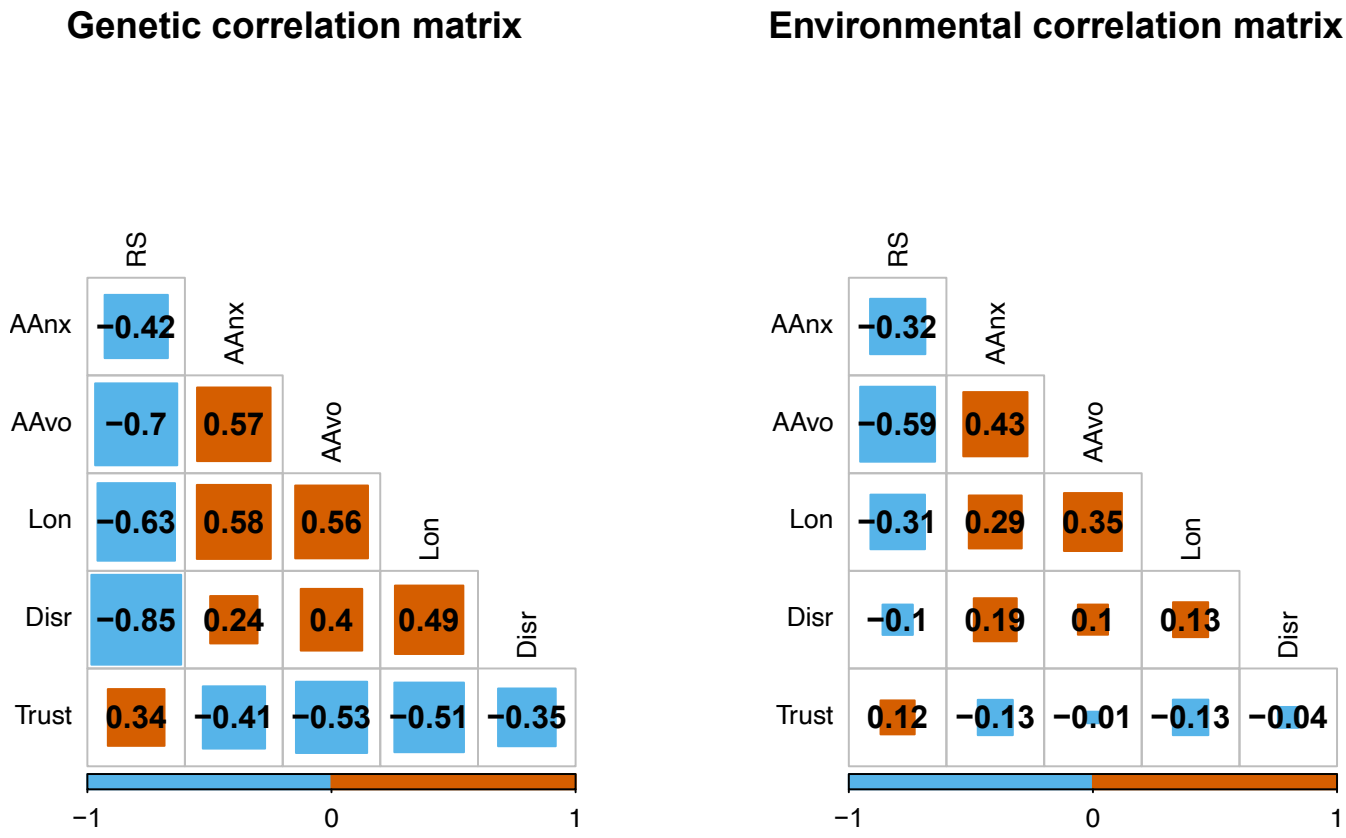


Paper 3: Multiple Social Factors are Associated With Wellbeing When Accounting for Shared Genetic and Environmental Confounding

In Paper 3, we examined genetic and environmental influences on and across social factors and associations with wellbeing when accounting for unmeasured familial confounding. The heritability estimates of the social factors ranged from 24% to 42%. There was substantial genetic overlap across the social factors. Multiple social factors were associated with concurrent wellbeing in within-pair estimates, although associations were attenuated compared with full sample associations, indicative of partial confounding. Relationship satisfaction, loneliness, and attachment avoidance were also associated with wellbeing six years later in within-pair estimates resulting from co-twin control analyses. Figure 3 displays the genetic and environmental correlations across social factors estimated in the multivariate AE Cholesky model. Figure 4 displays associations between social factors and wellbeing estimated in the co-twin control analyses.

Figure 3.

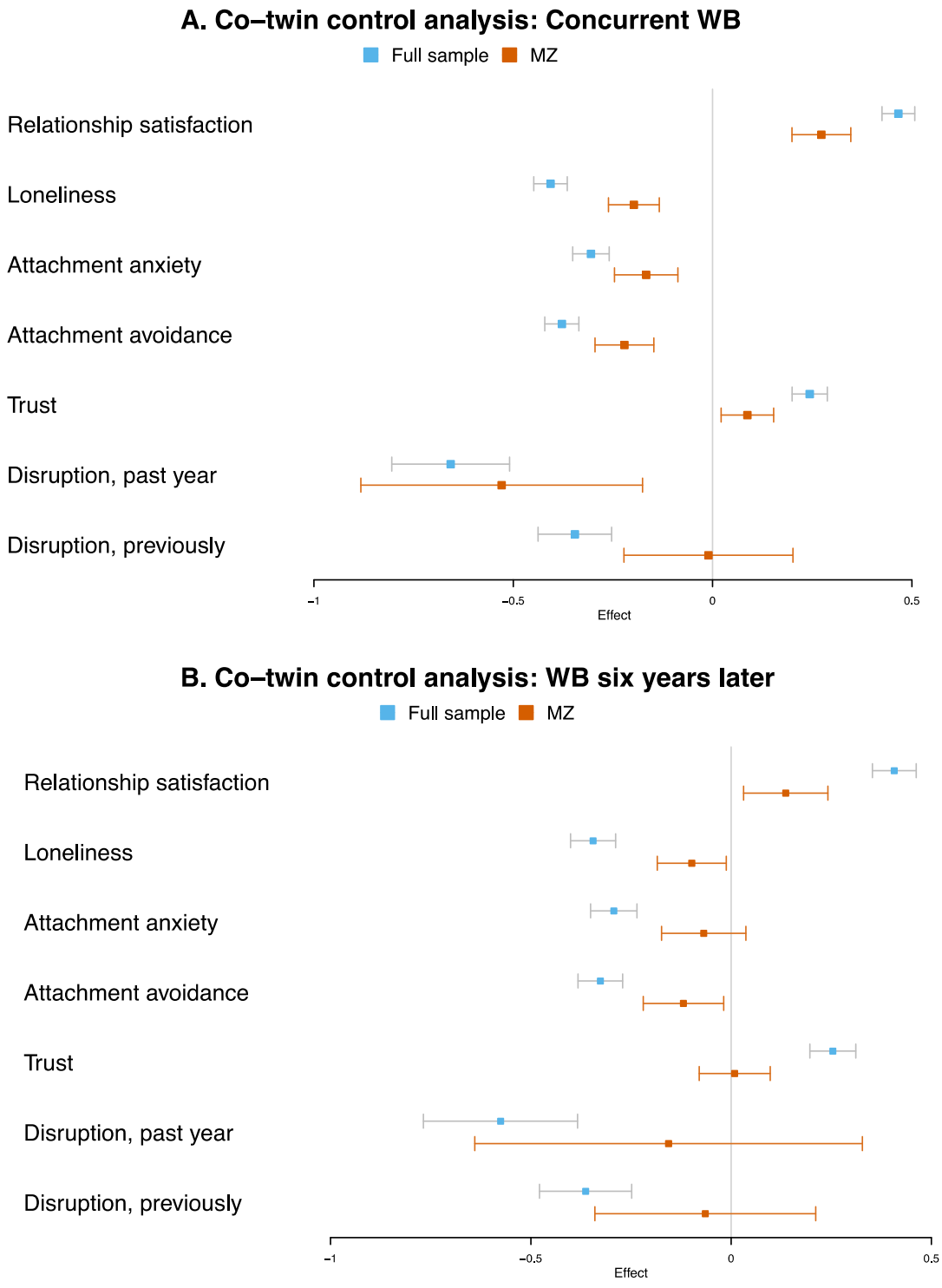
Genetic and Environmental Correlations From AE Cholesky Model.



Notes. 'RS' represents relationship satisfaction; 'AAnx' represents attachment anxiety; 'AAvo' represents attachment avoidance; 'Lon' represents loneliness; and 'Disr' represents disruptions in social relationships.

Figure 4.

Results of Co-Twin Control Analyses Examining Associations Between Social Factors and Wellbeing Measured Concurrently (A) and six Years Later (B).



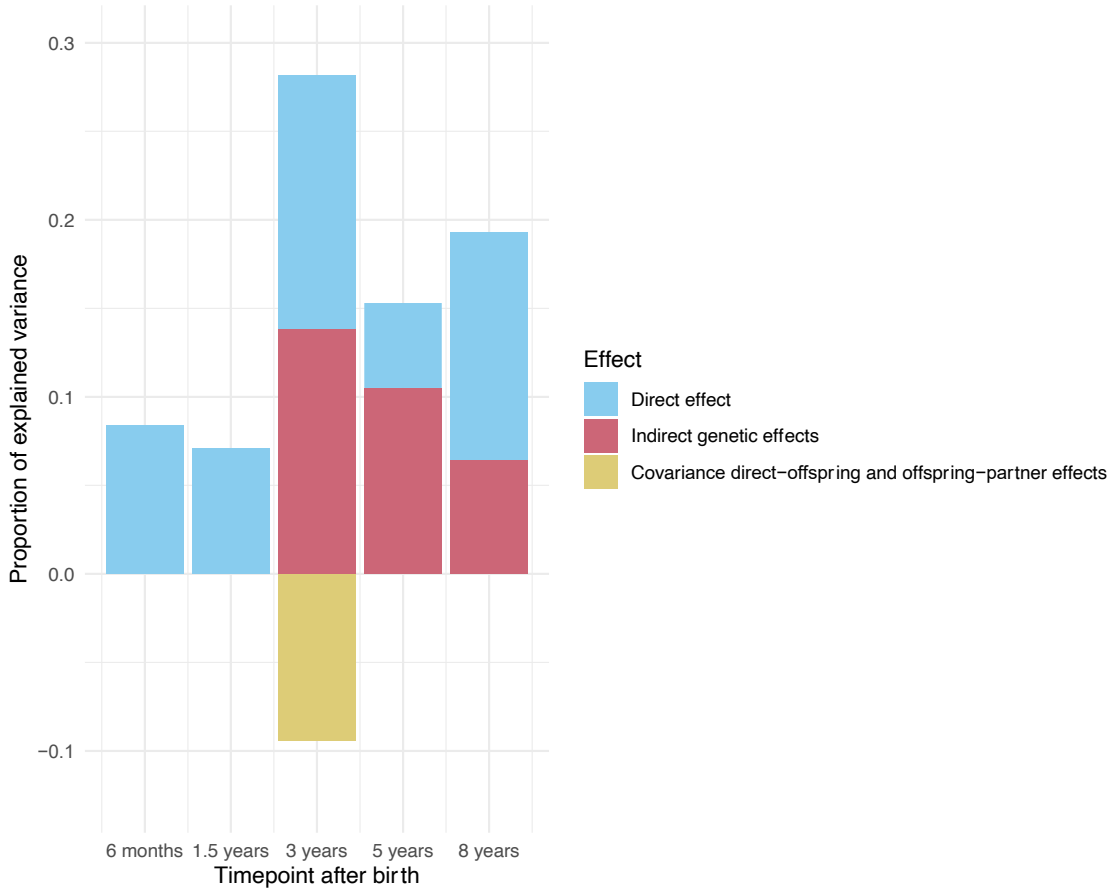
Notes. 'WB' represents wellbeing. 'MZ' refers to within-pair estimates for monozygotic twins. The error bars reflect 95% confidence intervals for the estimated effects.

Paper 4: Disentangling Direct and Indirect Genetic Effects From Partners and Offspring on Maternal Depression Using Trio-GCTA

In Paper 4, we quantified direct and indirect genetic effects from partners and offspring on maternal depressive symptoms across early childhood in a large sample of parent-offspring trios in MoBa with trio-GCTA. The variance explained by direct genetic effects ranged from 5% to 14% across the five timepoints after birth. The models with best fit at three timepoints after birth (3, 5, and 8 years) included indirect genetic effects. Indirect genetic effects explained 0% to 14% of variance across all timepoints. Figure 5 displays the variance explained by the standardized variance components at each timepoint (the remaining variance explained by residual error is not shown in Figure 5).

Figure 5.

Parameter Estimates From Trio-GCTA at Each Timepoint.



General Discussion

In this section, I discuss the findings of each paper in relation to each other. I subsequently discuss key findings of each paper in the context of the broader literature in which the papers are situated. Together, the findings shed light on genetic and environmental influences on wellbeing and illbeing (i.e., symptoms of anxiety and depression), as well as the importance of social factors for mental health in adulthood.

Insights Into Genetic Influences on Mental Health

The findings of three studies provided insights into genetic influences on wellbeing and symptoms of mental disorders, specifically. Wellbeing and depressive symptoms showed moderate genetic and substantial non-shared environmental influence, as did social factors. In Papers 1 and 3, we identified substantial overlap in genetic effects across several related traits using multivariate twin models—both multiple components of wellbeing and social factors. Thus, these findings highlight common genetic influences on interrelated complex phenotypes.

In Paper 4, we quantified the influence of a different type of genetic effects: those which depend on the genotypes of other people and are mediated through the environment. Such indirect genetic effects represent heritable traits in close family members which influence depressive symptoms in mothers. These intrafamilial influences also highlight how genes and environment are intricately linked—some environmentally mediated effects on maternal symptoms of depression are genetic in origin.

The Role of Environmental Factors

The findings of all three genetically informative studies (Papers 1, 3, and 4) showed that environmental factors explain the majority of variation in wellbeing, depressive symptoms, and social factors. These studies therefore not only clarify the role of genetic influences but also highlight the crucial role of the environment in explaining variation in

mental health and social factors. As previously noted, the findings of Paper 4 also showed that indirect genetic effects of close family members comprise one environmental risk factor for maternal depressive symptoms at multiple timepoints across early childhood.

The results of Paper 2 shed light on the multifactorial nature of associations between environmental factors and multiple aspects of mental health in the population. Environmental characteristics, ranging from the immediate housing environment to perceived aspects of society, showed complex interrelationships with each other and were jointly related to mental health.

The Importance of Social Factors

The findings of all four papers highlighted the importance of social factors for wellbeing and mental health. The structure of wellbeing identified in Paper 1 included social wellbeing as a distinct component, which exhibited a strong loading on the higher-order wellbeing factor. Accordingly, this suggests that social aspects may even be integral to the wellbeing construct itself. The networks estimated in Paper 2 revealed one key variable with particularly strong associations to all aspects of population mental health: how one perceives the social environment. Furthermore, recent experiences of discrimination, a stressful event intimately linked to society, was strongly related to poorer mental health.

The findings of Paper 3 provide evidence for the importance of social factors for wellbeing in adulthood, as associations between multiple social determinants and wellbeing remained substantial when accounting for unmeasured familial confounding. The findings of Paper 4 highlighted the importance of intrafamilial influences on maternal depressive symptom risk, which at least in part reflect indirect genetic effects from partners and offspring, at multiple timepoints after birth.

Robustness and Replicability of Findings

Two out of four papers (Papers 1 and 2) comprising this thesis specifically replicated the main analyses across independent samples, to examine the replicability of the findings. A landmark 2015 replication study found that only a third of studies in psychological research could be reproduced with statistically significant results in the same direction as in the original study (Open Science Collaboration, 2015). Issues related to replication and robustness of findings in psychological research have been discussed at length elsewhere (Munafò et al., 2017; Wiggins & Christopherson, 2019). For Papers 1 and 2, the main findings, both regarding the structure of wellbeing and mental health networks, were robustly replicated across multiple samples. This increases confidence in the reproducibility of the findings. The representativeness of the samples, which also has possible implications for generalizability, is further elaborated on in the section focusing on methodological considerations.

Paper 1: The Structure of Wellbeing: A Single Underlying Factor With Genetic and Environmental Influences

The Structure of Wellbeing Comprises Multiple First-Order Factors

Across more than 21,000 adults, we identified a factor model with six first-order components using hierarchical EFA. The model also had excellent fit in an independent sample. The identification of multiple first-order wellbeing factors is an agreement with previous studies which have reported good fit of models with several wellbeing components (e.g., Gallagher et al., 2009). All first-order factors loaded strongly on a higher-order wellbeing factor. While few studies have used hierarchical EFA, this is in partial agreement with previous investigations which have found that bifactor models with a general factor often provide good fit to data consisting of wellbeing items (Chen et al., 2013; Jovanović, 2015).

The identification of a higher-order wellbeing factor can also be viewed in light of developments in other areas of psychological research, such as the identification of the 'p-factor' in psychopathology research (Disabato et al., 2019). The p-factor represents a higher-order factor on which the dimensions of internalizing, externalizing, and thought disorder all load strongly (Caspi et al., 2014). Thus, the p-factor model exhibits similarities with our wellbeing model, in which multiple first-order factors loaded on a single higher-order factor.

The Structure of Wellbeing Comprises Both Hedonic and Eudaimonic Aspects

A continuing topic of debate in the wellbeing research field concerns the structure of wellbeing (Kashdan et al., 2008). Two widely influential theories of wellbeing are the SWB and PWB, which are typically conceptualised as hedonic and eudaimonic models of wellbeing, respectively. We found empirical support for including aspects of both hedonic wellbeing, such as positive affect, and eudaimonic wellbeing, such as experiencing that one is functioning well in the daily life, as part of the wellbeing construct. This is in agreement with previous studies which have reported very high correlation between hedonic and eudaimonic wellbeing (Kashdan et al., 2008).

Our study therefore does not provide support for a clear distinction between hedonic and eudaimonic models of wellbeing—aspects of both conceptualisations loaded strongly on the higher-order factor. Furthermore, genetic and environmental influences on all first-order factors were to a substantial extent shared across factors. Our findings provide partial support for more recent models of wellbeing which integrate components across the traditional theoretical distinction between hedonic and eudaimonic wellbeing (e.g., Forgeard et al., 2011; Seligman, 2018). This support is both phenotypic (i.e., provided in the factor analyses) and in terms of the structure of underlying genetic and environmental influences on wellbeing components.

The Structure of Wellbeing Includes Social Aspects

Some previous studies have emphasised the importance of social aspects of wellbeing and criticised previous work for not acknowledging the interpersonal nature of the construct (Keyes, 1998). Social aspects are not part of the original SWB model (Diener, 1984) but are conceptualised in the PWB model as 'positive relations with others' (Ryff, 1989). The findings of our study provide empirical support for the inclusion of social aspects when modelling the structure of wellbeing. This is also in agreement with recent models which explicitly include social factors as a wellbeing domain (e.g., Forgeard et al., 2011).

Need for Further Theoretical Work

Fried (2020) describes key issues in the factor and network literatures which deserve some consideration here. First, our findings should be interpreted in light of the problem of 'statistical equivalence', whereby competing models fitted to cross-sectional data, such as factor and network models, can explain the same observed data equally well. Thus, we can imagine that a network model in Paper 1 could yield equally good fit to the data as the hierarchical factor model. We can therefore not 'prove' the existence of the identified factor structure, including the higher-order wellbeing factor, because other models which have not been tested could provide equally good (or better) fit to the data.

A related point concerns the conflation of latent variables with psychological constructs, also highlighted by Fried (2020). The higher-order wellbeing factor we identified using factor analysis is a statistical construct. It is unclear what this statistical construct reflects and a (testable) theory explaining aspects of this construct would be needed to draw inferences regarding what the higher-order wellbeing factor 'is'. This lack of clarity is also reflected in the literature. A general wellbeing factor has previously been hypothesised to reflect 'overall perceived enjoyment and fulfillment with life' (Disabato et al., 2019), a

'positive orientation towards life' (Caprara et al., 2009), but could also reflect 'evaluation of negativity' (Böhnke & Croudace, 2016).

Paper 2: Mental Health and Environmental Factors in Adults: A Population-Based Network Analysis

Multiple Environmental Factors are Jointly Related to Population Mental Health

A key finding of Paper 2 was that the environmental factors which exhibited the strongest associations with population mental health were perceiving one's social environment positively and having recently experienced discrimination. This is broadly in agreement with the conclusions of previous syntheses of the literature, which have highlighted relationships between multiple aspects of social relations and wellbeing (Diener et al., 2018) and meta-analyses of associations between discrimination and mental health (Pascoe & Smart Richman, 2009; Schmitt et al., 2014). In addition, other environmental factors, from housing satisfaction and residential area characteristics to perceived influence on government, were also tied to mental health. Consequently, these findings underline the importance of several environmental characteristics for multiple aspects of population mental health.

The findings of this study also shed light on complex interrelationships between environmental factors and their *joint* relations to mental health, which few previous studies have explored. This provides partial support for the idea that environmental factors interact both with each other and with mental health, which, for instance, has been proposed is the case for urban factors in cities (van der Wal et al., 2021). We showed that connections between environmental factors and mental health occurs at multiple levels of aggregation of the latter—environmental factors display both associations with overall mental health constructs and individual symptoms.

Social Factors are key Variables in Mental Health Networks

As previously noted, positively perceiving one's social environment was strongly associated with better mental health. Various theories also argue the importance of social factors for mental health. Several models of wellbeing posit that positive social relationships is a key aspect of the wellbeing construct (Forgeard et al., 2011; Keyes, 1998; Ryff, 1989), with empirical support for this notion provided by the findings of Paper 1. The biopsychosocial model conceptualises risk of mental disorders as stemming from, in part, social determinants (Engel, 1977, 1980). Self-determination theory is another theoretical lens providing context for this finding, which emphasises connection with others as a fundamental human need (Ryan & Deci, 2017).Thus, this finding is in agreement with several influential psychological theories and models. The network analyses did not adjust for unmeasured familial confounding. As such, it is of relevance to note that the findings of Paper 4 provided further support for the importance of social factors for mental health in analyses which accounted for such potential confounding.

Environmental Factors at Multiple Levels are Related to Mental Health

We also found that perceptions of environmental factors at what can be conceived of as multiple levels were associated with population mental health. For instance, factors in the immediate environment, such as housing satisfaction, were associated with wellbeing. Perceptions of aspects of society, such as one's influence on government, were also associated with wellbeing. Influential models of environmental influences on human development, such as Bronfenbrenner's ecological systems theory, highlight the pervasive effects of environments occurring at more than one level (Bronfenbrenner, 1979, 2005).

Our study does not provide direct support for the importance of multi-level environmental influences as we examined associations between subjectively perceived environmental characteristics as opposed to objectively measured environmental factors.

Nevertheless, our findings show that perceived aspects of the environment, from more proximal aspects related to one's immediate living environment, to more distal aspects related to how one perceives societal institutions, are jointly connected to mental health in the population.

Paper 3: Multiple Social Factors are Associated With Wellbeing When Accounting for Shared Genetic and Environmental Confounding

Social Factors are Important Predictors of Wellbeing in Adulthood

Positive aspects of social relationships are included in several influential models and theories of wellbeing (Forgeard et al., 2011; Keyes, 1998; Ryff, 1989) and social determinants comprise one important component of the biopsychosocial model of mental health (Engel, 1977), as previously noted. The findings of Paper 4 support the notion that social factors are strongly associated with wellbeing, also when adjusting for unmeasured familial confounding. Our findings also indicate that several social factors are predictive of future wellbeing. Thus, these findings broadly underscore the importance of social factors for wellbeing in adulthood.

Unmeasured Familial Confounding may Bias Associations Between Social Factors and Wellbeing

A large literature has highlighted the importance of social factors for subjective wellbeing (Diener et al., 2018). Our findings also have implications for previous non-genetically informative studies, as we observe attenuation in within pair estimates compared with full sample associations, indicative of partial confounding by genetic and/or shared environmental factors. For instance, the effect size for the association between loneliness and wellbeing across studies is typically deemed 'large' (Park et al., 2020). In our study, this association was half of the full sample association within MZ twin pairs. This suggests that observed associations in previous non-genetically informative studies of social factors and

wellbeing could at least in part reflect bias from unmeasured familial confounding, such as genetic effects.

Genetic and Environmental Influences on Social Factors

We also identified moderate genetic and substantial non-shared environmental influence on social factors, in agreement with previous studies (e.g., Goossens et al., 2015; Kendler, 1997). Our study elaborates on these previous investigations by estimating genetic and environmental effects on and across multiple social factors.

These results are in agreement with a more general finding in genetically informative research—that measures which are typically conceived of as 'environmental' often reflect substantial genetic influence (Kendler & Baker, 2007). This genetic influence should be accounted for in studies which seek to examine associations between environmental factors and mental health. Our results also have implications for future studies which seek to identify SNPs associated with social factors. Substantial genetic correlation across social factors suggests that many genetic variants are common to perceptions of multiple aspects of the social environment and social phenotypes.

Paper 4: Disentangling Direct and Indirect Genetic Effects From Partners and Offspring on Maternal Depression Using Trio-GCTA

Direct and Indirect Genetic Effects Influence Maternal Depressive Symptoms

To our awareness, no previous studies have disentangled direct and indirect genetic effects on maternal depressive symptoms using trio-GCTA. We found that indirect genetic effects explained variance in maternal depressive symptoms at multiple timepoints after birth, in agreement with a previous MoBa study which also identified indirect genetic effects of partners and offspring on the same phenotype using a different statistical approach (Ayorech, Cheesman, et al., 2023). This finding also aligns with several studies which have identified 'genetic nurture' effects, which constitute genetic effects on child traits which are mediated

by parental behaviour (Cheesman et al., 2020; Eilertsen et al., 2022; Kong et al., 2018). Our findings suggest that indirect genetic effects from close family members also explain variance in maternal phenotypes, such as depressive symptoms.

The Intricate Connections Between Genes and Environment

Together, the results of Paper 4 highlight how genes and environment are linked to each other in complex ways. Traditional genetically informative methods are based on the decomposition of variance into genetic and environmental effects (i.e., estimates of A, D, C and E). However, some environmental effects reflect genetic effects mediated through the environment. These can be captured in GWAS studies which do not account for indirect effects (Young et al., 2019). Thus, findings from GWAS studies of maternal depressive symptoms could in part reflect indirect genetic effects and not only inherited genetic variants with causal impact on the phenotype. Our study also illustrates the utility of including families in genomic designs, which has been advocated for elsewhere (Cheesman et al., 2023).

The Importance of Close Family Members for Understanding Risk of Maternal Depressive Symptoms

In our study, indirect genetic effects indexed the impact of heritable traits in partners and offspring on maternal depressive symptom risk. Several influential theories of depression highlight the role of other people in influencing risk of depression. For instance, social support theory conceptualises the social support of family and other important people as a resource which can reduce risk of depression following adverse life events (Lakey & Cronin, 2008). Several psychotherapeutic treatments, such as interpersonal therapy, also emphasise the central role of relationships and interpersonal experiences for mental health (Frank & Spanier, 1995). While our findings are agnostic to which heritable traits in partners and offspring influence maternal depressive symptoms, the results provide strong support for the

role of close family members and intrafamilial influences on risk of depressive symptoms in mothers across early childhood.

Maternal Depression is a Family-Wide Mental Illness

The findings of Paper 4 also support the conceptualisation of maternal depression as a 'family-wide mental illness' (Ayorech, Cheesman, et al., 2023; Letourneau et al., 2012). Genetic effects of close family members are a risk factor for maternal depressive symptoms at multiple timepoints after birth. These effects may thus reflect family-level characteristics which influence risk of maternal depressive symptoms, in line with previous studies which have identified family-wide attributes associated with maternal depression (Madigan et al., 2017).

Ethical Considerations

There are important ethical considerations for all studies related to research participants' informed consent, responsible storage of research data, and the openness of statistical analyses and reproducibility of the findings, which have been underlined in current guidelines on research ethics in Norway (National Committee for Research Ethics in the Social Sciences and the Humanities, 2022). Informed consent and procedures for storage of data have been described previously. The data used in this thesis were not possible to share openly. I aimed to adhere to principles of open and reproducible science (Munafò et al., 2017) by sharing analysis code openly in the Supplementary Materials to the published articles or in public repositories on OSF for three out of four papers. This sharing of analysis code allowed for greater transparency and facilitated clarity and reproducibility of the work.

Dissemination of research findings is an integral part of the research process, also acknowledged in current ethical guidelines in Norway (National Committee for Research Ethics in the Social Sciences and the Humanities, 2022). There is a long history of misinterpretations, controversial applications, and misuse of findings from genetically

informative studies (Harden, 2023). The importance of sound communication of findings has also been highlighted in recent editorials in academic journals (e.g., 'Embracing Communication', 2021) and in a recent initiative aiming to promote socially responsible communication of findings from genetically informative research (Martschenko et al., 2021). A thorough discussion of this topic is beyond the scope of the current thesis. Nevertheless, important ethical considerations regarding how research findings in general, and from genetically informative studies specifically, are interpreted and communicated are critical. Such considerations underly the dissemination of findings from all studies comprising this thesis. I have aimed to report all findings accurately and transparently, while being mindful of their limitations and the importance of clearly conveying these.

Methodological Considerations

The findings of all papers comprising this thesis should be interpreted in light of some important methodological considerations, which I discuss in the following section.

Representativeness of the Samples, Selection Bias, and Attrition Bias

The representativeness of the samples deserves some scrutiny. All samples were sampled from a Western, Educated, Industrialised, Rich, and Democratic (WEIRD) context (Henrich et al., 2010), which limits generalizability. Furthermore, it is well-known from epidemiological research that both selection and attrition effects are often at play in large studies (Biele et al., 2019; Hernán et al., 2004). Selection effects occur when participants with particular characteristics are more likely to join a study. This is the case, for instance, for demographic and socioeconomic factors (Galea & Tracy, 2007). Attrition bias results when participants with certain characteristics have a higher probability of dropping out of longitudinal studies across timepoints. These forms of biases challenge the validity of epidemiological studies if non-participation and dropout are related to exposures and/or outcomes and limit external validity.

Several previous studies have indicated the presence of both selection and attrition bias in MoBa (Biele et al., 2019; R. M. Nilsen et al., 2009; Vejrup et al., 2022). The presence of modest selection effects has also been reported for a different NTR cohort previously (Tambs et al., 2009). As such, we cannot exclude the possible influence of bias from these sources on the findings of Papers 1, 3, and 4. Similarly, an overrepresentation in the final samples of individuals with certain characteristics was reported for QoL 2019, QoL 2020, and QoL 2021, in particular participants with higher education and a Norwegian country background (Pettersen & Støren, 2020, 2021; Støren & Todorovic, 2019). Thus, findings from Papers 1 and 2 should be interpreted taking this limitation into account.

Importantly, the genotype pipeline for MoBa only includes individuals with European ancestry genotype data (Corfield et al., 2022). Serious problems associated with current underrepresentation in genomic research have been thoroughly described elsewhere (Fatumo et al., 2022). This limitation implies that findings from Paper 4 cannot be generalised beyond the group which was studied, i.e., women with children, their partners, and a Norwegian context, based on European ancestry genotype data. Cheesman et al. (2023) argue that an important goal for future genomic research is to establish large family-based cohorts (like MoBa) which represent diverse ancestries.

An important assumption in twin studies is that twins are similar to non-twin individuals in the population for the given trait being studied (Kendler, Martin, et al., 1995; Plomin et al., 2013). If this assumption is not satisfied, findings from twin studies would only be generalizable to twins. In general, reporting of symptoms of common mental disorders has been found to be similar among twin and non-twin individuals (Kendler, Martin, et al., 1995). A recent review also concluded that twins are similar to singleton individuals for most traits (Hagenbeek et al., 2023).

Directionality in Associations and Recall Bias

The findings of Papers 2 and 3 also suffer from unclear directionality in observed associations. As both studies were primarily based on cross-sectional data, we cannot exclude the possibility that associations between two variables A and B may reflect: the influence of A → B; the influence of A ← B; or a combination of both. For instance, the association between relationship satisfaction and concurrent wellbeing observed in Paper 3 may reflect both the effect of the former on the latter but also the effect of the latter on the former. This is not an issue for the findings of Paper 4. Although the analyses were cross-sectional at each timepoint, indirect genetic effects were derived from genomic data. Given that depressive symptoms in one person cannot alter the DNA of another person, this eliminates the risk of reverse confounding.

The possible influence of recall bias, i.e., if current mood states (e.g., high levels of wellbeing or depressive symptomatology) affect reporting of items, is an important limitation of Papers 2 and 3. This limitation is particularly salient for Paper 2. For instance, it is possible that individuals with higher depressive symptomatology report certain environmental characteristics, such as lower satisfaction with housing, due to the depressive symptoms themselves. Therefore, this association could at least in part reflect higher symptom levels rather than an effect of housing satisfaction on depressive symptoms. The influence of recall bias on associations between social factors and wellbeing measured six years later in Paper 3 was partially remedied as social factors were measured at a previous timepoint.

The Equal Environments Assumption in the Classical Twin Design

An important assumption in the CTD (applied in Papers 1 and 3) is that MZ and DZ twins are treated similarly in the environment (Plomin et al., 2013), i.e., that the correlation for phenotypically relevant environmental exposures among both types of twins is similar (Kendler et al., 1993). If this assumption does not hold, increased similarity among MZ twins

could reflect environmental effects in addition to genetic effects (if MZ twins are treated in more similar ways compared with DZ twins). The equal environments assumption seems valid for mental disorders, including depression (Kendler et al., 1993, 1994). Røysamb et al. (2014) concluded that genetically informative studies of wellbeing thus far have not provided evidence of violations of this assumption.

The Assumption of Random Mating in the Population

An assumption in both the CTD and trio-GCTA is that mating patterns in the population are random. Assortative mating, i.e., non-random mating patterns whereby some individuals are more likely to choose partners with similar traits, could in the CTD lead to DZ twins sharing more than 50% of their genetic material and bias estimated parameters (Coventry & Keller, 2005). It is currently not clear how such bias should be reflected in inferences drawn on the basis of trio-GCTA analyses (Eilertsen et al., 2021).

Non-random mating is pervasive for many traits in the population, including phenotypes related to those studied in the papers comprising this thesis. For instance, correlations among partners have been reported at .19 for generalized anxiety disorder (Peyrot et al., 2016), .18 for symptoms of major depression in MoBa (Torvik et al., 2022), and at .26 for SWB in another Norwegian sample (Nes, Czajkowski, et al., 2010).

In spite of its occurrence, Peyrot et al. (2016) argued that bias in heritability estimates which reflects assortative mating is unlikely to be large with respect to psychiatric disorders. Røysamb et al. (2014) concluded that there were no indications of substantially biased parameters in twin studies of wellbeing resulting from assortative mating, which can also be accounted for in extended twin designs.

The findings of two recent MoBa studies which used polygenic score analyses suggest that assortative mating may not be widespread for depressive symptoms in this cohort. One did not find evidence of partner correlations for a general genetic factor reflecting liability to

all mental disorders (Ayorech, Torvik, et al., 2023), whereas the other did not identify assortative mating for psychiatric traits, including depression (Sunde et al., 2023).

Population Stratification

Population stratification occurs when allele frequencies differ within populations, which can bias genomic studies (Cardon & Palmer, 2003). Using principal components of SNPs as covariates is a frequently used method to correct for population stratification (Price et al., 2010). While we used principal components of mothers and partners as covariates in Paper 4, future studies should examine the extent to which direct and indirect genetic effect estimates from trio-GCTA analyses may reflect uncorrected bias from population stratification (Eilertsen et al., 2022).

The Assumption of Non-Additivity in Genetic Effects

An assumption in the trio-GCTA method is that genetic effects (both direct and indirect) are additive, i.e., that effects of alleles 'sum up' in their effects on a phenotype (Eilertsen et al., 2021). Non-additive genetic effects and interactions between direct and indirect effects would violate this premise. A similar assumption was also made in all final twin models, whereby the 'D' effects were set to 0 after comparing the fit of multiple models, some of which included non-additive effects. Thus, if minor non-additive genetic effects were present, these would not be identified in Papers 1, 3, and 4, and would bias the estimated parameters. Previous twin studies of depression have not found substantial evidence of non-additive genetic effects (e.g., Kendler et al., 1992). For wellbeing, well-powered extended twin studies have detected non-additive genetic effects (Bartels, 2015).

Measurement Error

Although most scales and measures used across Papers 1-4 were validated and/or have been previously used in other studies, we cannot exclude the possible influence of measurement error on the results. Measurement error (together with non-shared confounding)

represent threats to valid parameter estimates and inferences in co-twin control designs (Frisell et al., 2012). The network analyses in Paper 2 also did not model measurement error, which can affect network structure (Borsboom et al., 2021). However, one recent simulation study found that the influence of measurement error on single-indicator networks is less serious at larger sample sizes (de Ron et al., 2022). Nevertheless, we did not quantify measurement error in the studies conducted as part of this thesis and cannot rule out potential bias arising from this source.

Recommendations for Future Research

I briefly outline some suggestions for future research based on the papers comprising this thesis in the following section. First, future studies could focus on examining the extent to which influences on wellbeing and illbeing are common or unique. For instance, future studies could examine the extent to which the higher-order wellbeing factor and the p-factor capture similar aspects of mental health and potential overlap in their genetic and environmental influences. Furthermore, future studies could apply trio-GCTA to examine direct and indirect genetic effects on maternal wellbeing in the postpartum period and the extent to which these correspond with effects on maternal depressive symptoms.

Increasingly, it has been acknowledged that psychological research as a discipline is facing serious challenges regarding its theoretical underpinnings (Eronen & Bringmann, 2021; Fried, 2020). Importantly, the need to support both factor and network analysis work with theories concerning the statistical constructs which are identified has been highlighted elsewhere (Fried, 2020). Similar notions regarding the importance of how data and theory can support each other have been emphasised in relation to wellbeing research specifically (Kashdan et al., 2008). A useful aim for future studies would be to advance theoretical work concerning both the conceptualisations of wellbeing and mental disorders, as well as their underlying influences.

Importantly, most analyses in the papers comprising this thesis were based on cross-sectional data. Therefore, studies based on data with repeated measurements could extend our findings in multiple ways. Few studies have examined the development of general wellbeing constructs across time and genetic and environmental contributions to their stability and change. Longitudinal network models could provide important insights into the dynamics of environmental factors and mental health across time. Such network models could be applied to both panel data and intensive longitudinal data. Longitudinal analyses with genetically informative samples (e.g., genetically informative random-intercept cross-lagged panel models) could provide insights into associations between social factors and wellbeing, their co-development, and genetic and environmental contributions to these. Future studies could also examine stability of indirect genetic effects on maternal depressive symptoms throughout childhood and the extent to which the same SNPs influence maternal depressive symptoms over several timepoints.

We applied multiple research designs and statistical methods, including both genetically informative approaches and network analysis, to answer the research questions. Triangulating the results of longitudinal network studies with genetically informative designs which can account for unmeasured confounding, such as sibling control studies, could help identify environmental factors with probable causal influence on mental health in the population. Furthermore, future studies combining both self-report and registry-based data across time, between countries, and at multiple levels within countries (e.g., counties, municipalities, and cities), could also provide further insights into multilevel and time-varying environmental effects on mental health.

As previously noted, all samples were from a WEIRD context, limiting the generalizability of findings. Future studies could examine general wellbeing factors using different items and scales and in non-WEIRD contexts. Future studies could also apply the

trio-GCTA approach to quantify direct and indirect genetic effects in more diverse samples, which would advance current understanding of genetic and environmental effects on maternal depressive symptoms. We also used a relatively narrow operationalization of wellbeing in Paper 3 (i.e., based on the SWB model). As the findings of Paper 1 supported the modelling of wellbeing as a multi-component construct, future studies could examine associations between social factors and broader conceptualisations of wellbeing.

Conclusion

The overarching aim of this thesis was to advance current understanding of genetic and environmental effects, including the role of social factors, on wellbeing and illbeing (i.e., symptoms of anxiety and depression). Our findings provided new insights into genetic influences on mental health, including genetic effects on wellbeing components and maternal depressive symptoms, and on social factors. Our findings also shed light on the role of the environment: the majority of individual differences in mental health was accounted for by environmental effects in all genetically informative studies. Furthermore, environmental factors exhibited complex associations with multiple aspects of mental health as well as other environmental characteristics in network analyses, and multiple social factors were strongly associated with wellbeing when accounting for unmeasured familial confounding. Indirect genetic effects, which reflect environmental influences of genetic origin, affect maternal depressive symptom risk at multiple timepoints after birth. The findings of all four studies highlighted the importance of social factors for mental health in adulthood.

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Appendix A

All items used in Paper 1 are reported in this appendix.

Table A1.

Wellbeing Items included in the EFA and CFA.

Item no.	Question text	Scale or single item
Q1	In most ways my life is close to my ideal.	SWLS[1]
Q2	The conditions of my life are excellent.	SWLS[1]
Q3	I am satisfied with life.	SWLS[1]
Q4	So far I have gotten the important things I want in life.	SWLS[1]
Q5	If I could live my life over, I would change almost nothing.	SWLS[1]
Q6	How often do you experience being interested in what you are doing?	ESS[2]
Q7	How often do you experience being absorbed in what you are doing?	ESS[2]
Q8	How often do you experience being enthusiastic about what you are doing?	ESS[2]
Q9	I've been feeling optimistic about the future.	WEMWBS[3]
Q10	I've been feeling useful.	WEMWBS[3]
Q11	I've been feeling relaxed.	WEMWBS[3]
Q12	I've been dealing with problems well.	WEMWBS[3]
Q13	I've been thinking clearly.	WEMWBS[3]
Q14	I've been feeling close to other people.	WEMWBS[3]
Q15	I've been able to make up my own mind about things.	WEMWBS[3]
Q16	I have little control over what happens to me.	Mastery scale[4]
Q17	Some of my problems I simply cannot solve.	Mastery scale[4]
Q18	There is little I can do to change aspects of my life that are important.	Mastery scale[4]
Q19	When faced with problems in my life I often feel helpless.	Mastery scale[4]
Q20	Sometimes it feels like I am only pushed around in life.	Mastery scale[4]
Q21	Overall, how satisfied are you with your life at the moment?	OECD[5,7]
Q22	Overall, to what extent do you experience what you're doing in life as worthwhile?	OECD[5,7]
Q23	In the last 7 days, to what extent have you been happy?	Adapted from OECD[5,7]
Q24	In the last 7 days, to what extent have you been worried?	Adapted from OECD[5,7]
Q25	In the last 7 days, to what extent have you been feeling down or sad?	Adapted from OECD[5,7]
Q26	My social relations are supportive and rewarding.	Flourishing scale[6]
Q27	I actively contribute to the happiness and well-being of others.	Flourishing scale[6]
Q28	Do you think your life is mostly full of experiences and rich, or mostly empty and boring?	Single-item[7]
Q29	Overall, how happy with your life do you think you will be in 5 years?[8]	Single-item[7]
Q30	In the last 7 days, to what extent have you been irritated?	Single-item[7]
Q31	In the last 7 days, to what extent have you been invested/engaged?	Single-item[7]
Q32	In the last 7 days, to what extent have you been calm and relaxed?	Single-item[7]
Q33	In the last 7 days, to what extent have you been anxious?	Single-item[7]
Q34	In the last 7 days, to what extent have you been stressed?	Single-item[7]
Q35	How happy are you with your relationship with your children?	Single-item[7]
Q36	How happy are you with your relationship with your friends?	Single-item[7]
Q37	How happy are you with your relationship with your partner?	Single-item[7]

Notes.[1]Satisfaction with Life Scale (Diener et al., 1985); [2]European Social Survey (2013); [3]The Warwick-Edinburgh Mental Well-being Scale (Tennant et al., 2007); [4]The Mastery Scale (Pearlin & Schooler, 1978); [5]OECD (2013); [6]The Flourishing Scale (Diener et al., 2009); [7]These items have been recommended for national monitoring of wellbeing in the Norwegian population (Nes et al., 2018). [8]This item was not a part of the QoL 2020 survey and therefore only included in the EFA.

Table A2.

Items in the Norwegian Twin Registry 1945-1960 Cohort.

Item code	Question
S_22_1	In most ways my life is close to my ideal.
S_22_2	The conditions of my life are excellent.
S_22_3	I am satisfied with my life.
S_22_4	So far I have gotten the important things I want in life.
S_22_5	If I could live my life over, I would change almost nothing.
S_23	Overall, would you say that what you are doing in life is worthwhile?
S_24_1	Have you been bothered by any of the following during the last two weeks: being afraid or anxious.
S_24_2	Have you been bothered by any of the following during the last two weeks: Nervousness or shakiness inside.
S_24_3	Have you been bothered by any of the following during the last two weeks: Feeling hopeless about the future.
S_24_4	Have you been bothered by any of the following during the last two weeks: Feeling blue.
S_24_5	Have you been bothered by any of the following during the last two weeks: Worrying too much about things.
S_24_6	Have you been bothered by any of the following during the last two weeks: Feeling like everything is an effort.
S_24_7	Have you been bothered by any of the following during the last two weeks: Felt tense or keyed up.
S_24_8	Have you been bothered by any of the following during the last two weeks: Suddenly scared for no reason.
S_25_1_1	How often do you experience the following in your everyday life: Feel glad about something.
S_25_1_2	How often do you experience the following in your everyday life: Feel happy.
S_25_1_3	How often do you experience the following in your everyday life: Feel joyful, like everything is going your way.
S_26_1	I can always manage to solve difficult problems if I try hard enough.
S_26_2	If I am in trouble, I can usually think of a solution.
S_26_3	If someone opposes me, I can find the means and ways to get what I want.
S_26_4	I am confident that I could deal efficiently with unexpected events.
S_26_5	I can remain calm when facing difficulties because I can rely on my coping abilities.
S_31_1	In uncertain times, I usually expect the best.
S_31_2	If something can go wrong for me, it will.
S_31_3	I am always optimistic about my future.
S_31_4	I hardly ever expect things to go my way.
S_31_5	I rarely count on good things happening to me.
S_31_6	Overall, I expect more good things to happen to me than bad.
S_32_1	I am very happy with our relationship.
S_32_2	My partner and I have problems in our relationship.
S_32_3	My partner is generally understanding.
S_32_4	I am satisfied with my relationship with my partner.
S_32_5	We agree on how children should be raised.

Table A3.

Scales and Response Formats for Items in the Norwegian Twin Registry 1945-1960 Cohort.

Item codes	Scale	Response format
S_22_1, S_22_2, S_22_3, S_22_4, S_22_5	SWLS[1]	Totally disagree (1) - Totally agree (7)
S_23	OECD[2]	Not meaningful at all (0) - Very meaningful (10)
S_31_1, S_31_2, S_31_3, S_31_4, S_31_5, S_31_6	LOT-R[3]	Totally disagree (1) – Totally agree (5)
S_24_1, S_24_2, S_24_3, S_24_4, S_24_5, S_24_6, S_24_7, S_24_8	SCL-8[4]	Not bothered (1) – Very much bothered (4)
S_25_1_1, S_25_1_2, S_25_1_3	DES[5]	Rarely/Never (1) – Very often (5)
S_26_1, S_26_2, S_26_3, S_26_4, S_26_5	GSE[6]	Not correct (1) – Totally correct (4)
S_32_1, S_32_2, S_32_3, S_32_4, S_32_5	RSS[7]	Strongly disagree (1) – Strongly agree (6)

Notes. [1]Satisfaction with Life Scale (Diener et al., 1985), [2]OECD (2013), [3]Revised Life Orientation Test (Scheier et al., 1994), [4]Symptom Checklist-8 (Tambs & Røysamb, 2014), [5]Differential Emotions Scale (Izard et al., 1993), [6]General Self-Efficacy Scale (Leganger et al., 2000; Tambs & Røysamb, 2014), [7]Relationship Satisfaction Scale (Røysamb, Vittersø, et al., 2014). Some items were recoded so that all items reflected higher wellbeing (i.e., these items were reversed). Recoded items were: S_24_1, S_24_2, S_24_3, S_24_4, S_24_5, S_24_6, S_24_7, S_24_8, S_31_2, S_31_4, S_31_5, S_32_2.

Appendix B

All SWLS, SCL items, and environmental characteristics used in Paper 2 are reported in this appendix.

Table B1.

All Self-Report Items.

Item Code	Question	Response format	Variable coding format
—	Satisfaction With Life Scale items	Completely Disagree - Completely Agree	Completely Disagree (1) - Completely Agree (7)
SWLS1	In most ways my life is close to my ideal.	—	—
SWLS2	The conditions of my life are excellent.	—	—
SWLS3	I am satisfied with life.	—	—
SWLS4	So far I have gotten the important things I want in life.	—	—
SWLS5	If I could live my life over, I would change almost nothing.	—	—
Social	My social relations are supportive and rewarding.	Totally disagree - Totally agree	Totally disagree (0) - Totally agree (10)
PlaceSatisf	How happy are you with the place (area/village/district) you live?	Not happy at all - Very happy	Not happy at all (0) - Very happy (10)
HomeSatisf	How happy are you with your housing?	Not happy at all - Very happy	Not happy at all (0) - Very happy (10)
Belonging	To what extent do you feel a sense of belonging to where you live?	No sense of belonging - Strong sense of belonging	No sense of belonging (0) - Strong sense of belonging (10)
Noise	When you are inside your home, do you have problems with: Noise from neighbours or other noise from outside, e.g., from traffic, industry or facilities?	Yes / No	No (0) - Yes (1)
Contamin	When you are inside your home, do you have problems with: dust, smell or other contamination in the area round your home because of traffic, industry or businesses?	Yes / No	No (0) - Yes (1)
PlayRecr	Is there an area which can be used for play and recreation within 200 meters from your home?	Yes / No	No (0) - Yes (1)

Hike	Is there hiking terrain within 500 meters from your home?	Yes / No	No (0) - Yes (1)
Safe	Overall, how safe do you feel when you are out walking in your local environment?	Not safe at all - Very safe	Not safe at all (0) - Very safe (10)
Crime	Do you have problems with crime, violence or vandalism in your residential area?	Yes / No	No (0) - Yes (1)
WorriedResArea	Have you lately been worried about experiencing violence or threats when walking outside and alone where you live?	Not worried / Somewhat worried/ Very worried	Not worried (0) - Somewhat or very worried (1)
GovernInfluence	To what extent would you say the political system in Norway gives people like you influence over what the government is doing?	Not at all - To a very large extent	Not at all (0) - To a very large extent (10)
Discrimin	Have you, in the last 12 months, experienced being treated worse than others because of: age, gender, health problems/illness/injury, disability, ethnic background, skin color, religion, political attitudes, sexual identity, unclear reason?	Yes / No	No (0) - Yes (1)
TrustIllDis[a]	How safe do you feel that the public sector will give you the help you need: in case of becoming ill or injured.	Not safe at all - Very safe	Not safe at all (0) - Very safe (10)
TrustIllDis[a]	How safe do you feel that the public sector will give you the help you need: in case of becoming unable to work.	Not safe at all - Very safe	Not safe at all (0) - Very safe (10)
Gender	What gender do you identify as?	Male / Female / Other / Do not wish to answer	Male (0) - Female (1)
SexOrient	Do you consider yourself being:	Heterosexual / Gay or lesbian / Bisexual / Other / Do not know / Do not wish to answer	Heterosexual (0) - Other (1)
—	Hopkins Symptom Checklist items: Have you been bothered by any of the following during the last two weeks?	Not Bothered - Very Bothered	Not Bothered (1) - Very Bothered (4)
Nervous	Nervousness or shakiness inside	—	—
Fearnoreason	Suddenly scared for no reason	—	—
Afraid	Feeling fearful	—	—
Insomnia	Sleeping problems	—	—
Hopelessness	Feeling hopeless about the future	—	—
Feelingblue	Feeling blue	—	—
Worried	Worrying too much about things	—	—

Notes. [a]The responses for these two items were combined and a mean score was calculated.

Table B2.

Characteristics of Environmental Nodes Included in Networks.

Environmental characteristic	Response format	Self-report or registry
Supportive and rewarding social relations	0-10 rating scale	Self-report
Satisfaction with area/village/district	0-10 rating scale	Self-report
Satisfaction with housing	0-10 rating scale	Self-report
Sense of belonging to residential area	0-10 rating scale	Self-report
Household crowding (number of people in household divided by number of rooms)[a]	—	Registry-data
Feeling safe when out walking in the local environment	0-10 rating scale	Self-report
Trust in help from the public sector if becoming ill, injured or unable to work[b]	0-10 rating scale (mean score)	Self-report
Perceived influence on government	0-10 rating scale	Self-report
Problems with noise at home	Binary (yes/no)	Self-report
Problems with dust, smell or contamination at home	Binary (yes/no)	Self-report
Area for play and recreation within 200 metres of home	Binary (yes/no)	Self-report
Area for hiking within 500 metres of home	Binary (yes/no)	Self-report
Problems with crime, violence or vandalism in residential area	Binary (yes/no)	Self-report
Worried about violence or threats when walking outside and alone[c]	Binary (Very or somewhat worried/Not worried)	Self-report
Experienced discrimination in the last 12 months (for any reason)[d]	Binary (yes/no)	Self-report
Living in a rural or urban area	—	Registry-data

Notes. [a]Number of people in household was a truncated variable ranging from one to five or more; number of rooms was truncated and ranged from one to 10 or more. [b]This was the mean score of two items assessing trust that the public sector would provide help needed if becoming ill or injured (item 1) and if becoming unable to work (item 2). [c]The responses for this item were recoded to a binary format as reported. The original response options were "Very worried", "Somewhat worried" and "Not worried". [d]This item was an aggregate of multiple binary items (with response options "Yes" and "No") assessing recent experiences of discrimination because of: age, gender, health problems or illness or injury, disability, ethnic background, skin colour, religion, political attitudes, sexual identity, other reason or uncertain reason. Binary environmental characteristics were coded so 0 represented the absence and 1 the presence of the characteristic. Living in a rural area was coded 0 and urban area coded 1.

Appendix C

All items used in Paper 3 and their response formats are reported in Appendix C.

Item text	Response format	Scale or construct
In most ways my life is close to my ideal.	Totally disagree (1) - Totally agree (7)	SWLS[1]
The conditions of my life are excellent.	Totally disagree (1) - Totally agree (7)	SWLS[1]
I am satisfied with life.	Totally disagree (1) - Totally agree (7)	SWLS[1]
So far I have gotten the important things I want in life.	Totally disagree (1) - Totally agree (7)	SWLS[1]
If I could live my life over, I would change almost nothing.	Totally disagree (1) - Totally agree (7)	SWLS[1]
I am very happy with our relationship.	Strongly disagree (1) – Strongly agree (6)	RSS[2]
My partner and I have problems in our relationship.	Strongly disagree (1) – Strongly agree (6)	RSS[2]
My partner is generally understanding.	Strongly disagree (1) – Strongly agree (6)	RSS[2]
I am satisfied with my relationship with my partner.	Strongly disagree (1) – Strongly agree (6)	RSS[2]
We agree on how children should be raised.	Strongly disagree (1) – Strongly agree (6)	RSS[2]
Divorce, separation or termination of cohabitation	No (0) - Yes (1)	Disruptions in social relationships
Large conflicts in the partner relationship	No (0) - Yes (1)	Disruptions in social relationships
Problems or large conflicts with family, friends or neighbours	No (0) - Yes (1)	Disruptions in social relationships
I worry about being abandoned	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I am very comfortable being close to my partner emotionally.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]

I worry a lot about my relationships.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I worry that my partner won't care as much as I do	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I worry a fair amount about losing my partner	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I don't feel comfortable opening up to my partner	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I want to get close to my partner, but I keep pulling back.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I get nervous when my partner gets too close to me.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I avoid getting too close to my partner.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I find it difficult to depend on my partner.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
If I can't get my partner to show interest in me, I get upset.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
When I'm not involved in a relationship, I feel insecure.	Strongly disagree (1) – Strongly agree (7)	ECR-N12[3]
I feel isolated from others	Never (1) - Always (5)	UCLA Loneliness Scale[4]
I lack companionship	Never (1) - Always (5)	UCLA Loneliness Scale[4]
I feel left out	Never (1) - Always (5)	UCLA Loneliness Scale[4]
Generally speaking, would you say that most people can be trusted or that you can't be too careful in dealing with people?	You cannot be too careful (0) - Most people can be trusted (10)	ESS[5]
Do you think that most people would try to take advantage of you if they got the chance, or would they try to be fair?	Most people would try to take advantage of me (0) – Most people would try to be fair (10)	ESS[5]
Would you say that most of the time people try to be helpful or that they are mostly looking out for themselves?	People are mostly looking out for themselves (0) – People mostly try to be helpful (10)	ESS[5]

Notes. [1]Satisfaction with Life Scale (Diener et al., 1985); [2]Relationship Satisfaction Scale (Røysamb et al., 2014); [3]Experiences in Close Relationship Scale (Olssøn et al., 2010); [4]Hughes et al. (2004); [5]European Social Survey (OECD, 2017).

Erratataliste

Navn kandidat: Ludvig Daae Bjørndal

Avhandlingstittel: Unravelling sources of wellbeing and illbeing: The role of genetic, environmental, and social factors

Side	Linje	Fotnote	Originaltekst	Type rettelse	Korrigert tekst
viii	17		Disentangling direct and indirect genetic effects from partners and offspring on maternal depression using trio-GCTA. *Nature Mental Health*.		Disentangling direct and indirect genetic effects from partners and offspring on maternal depression using trio-GCTA. *Nature Mental Health*. https://doi.org/10.1038/s44220-024-00207-3

I

Quality of Life Research
https://doi.org/10.1007/s11136-023-03437-7

The structure of well-being: a single underlying factor with genetic and environmental influences

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Accepted: 5 May 2023

Abstract

Purpose The structure of well-being has been debated for millennia. Dominant conceptualisations, such as the hedonic and eudaimonic models, emphasise different constituents of the well-being construct. Some previous studies have suggested that the underlying structure of well-being may consist of one or a few general well-being factors. We conducted three studies to advance knowledge on the structure of well-being comprising more than 21,500 individuals, including a genetically informative twin sample.

Methods In Study 1, we used hierarchical exploratory factor analysis to identify well-being factors in a population-based sample of Norwegian adults. In Study 2, we used confirmatory factor analysis to examine the model fit of the identified factor model in an independent sample. In Study 3, we used biometric models to examine genetic and environmental influences on general well-being factors.

Results We identified six well-being factors which all loaded on a single higher-order factor. This higher-order factor may represent a general "happiness factor", i.e. an *h-factor*, akin to the *p-factor* in psychopathology research. The identified factor model had excellent fit in an independent sample. All well-being factors showed moderate genetic and substantial non-shared environmental influence, with heritability estimates ranging from 26% to 40%. Heritability was highest for the higher-order general happiness factor.

Conclusion Our findings yield novel insights into the structure of well-being and genetic and environmental influences on general well-being factors, with implications for well-being and mental health research, including genetically informative studies.

Keywords Well-being · Genetics · Environment · Happiness · Well-being factors · h-factor

Introduction

What is happiness? This question has been asked for millennia and is an important topic in many philosophical and religious traditions. For instance, Aristotle's writings on eudaimonia represent an early, yet still influential, inquiry into the structure of well-being [1]. Well-being is also an important theme in stoic [2] and Confucian (R. [3] philosophy. These different traditions emphasise different aspects of well-being—yet all are concerned with the question of what well-being encompasses.

The structure of well-being is also a topic of debate in research. Gallagher et al. [4] broadly distinguish between hedonic, eudaimonic, and social well-being models. A prominent example of a hedonic model is the subjective well-being (SWB) model, comprising pleasant affect, (absence of) unpleasant affect, and life satisfaction [5–7]. Life satisfaction has also been conceptualised as a core indicator of evaluative well-being [8]. The eudaimonic Psychological Well-being (PWB) model was proposed by Ryff [9]. It includes six components: self-acceptance, positive relations with others, autonomy, environmental mastery, a sense of

The manuscript has been posted as a preprint on PsyArXiv and can be accessed via the following https://doi.org/10.31234/osf.io/mzp3r.

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Published online: 20 May 2023

purpose in life, and personal growth. Both frameworks have spawned much research [6, 10]. Other models emphasise the importance of social aspects of well-being (e.g. see Ref [11].

More recent approaches have attempted to integrate components from theoretically distinct well-being models. For instance, Keyes [12] included aspects of hedonic, eudaimonic, and social well-being in the 'flourishing mental health' model. Another recent model included five components: positive emotion, engagement, relationships, meaning, and accomplishment (PERMA) [13, 14]. Integrative efforts are supported by studies showing that hedonic and eudaimonic well-being are highly correlated (e.g. [15–17], even though they are theoretically assumed to capture different aspects of well-being.

Recent years have seen a development towards a hierarchical framework in well-being research, mirroring other areas of psychological science [18]. Several studies have found that a few general factors largely explain variance in well-being items in hierarchical and bifactor models (e.g. see Refs [4, 15, 16, 19–22] and that models with a single factor may show similarly good or superior fit to the data [23–25, 27]. These studies converge to suggest that the underlying structure of well-being may consist of one or a few general well-being factors. Recent studies have also examined well-being structure using a network psychometric approach (e.g. see Refs [28, 29].

Several questions pertaining to a hierarchical framework for well-being remain unresolved. First, there are inconsistencies in the numbers of identified well-being factors across studies. Second, few studies have used items from multiple well-being measures and conceptual frameworks. Third, many studies suffer from small sample sizes and low statistical power. Fourth, most studies have tested predefined theoretical models using confirmatory factor analysis (CFA). Combining CFA with data-driven approaches, such as exploratory factor analysis (EFA), could yield new insights into well-being factors. This has only been done in a small number of studies (e.g. see Ref [17, 20, 30].

Elucidating the structure of general well-being factors could have implications for theoretical models and development. Furthermore, well-being is measured in a myriad of ways [18, 31, 32]. Heterogeneous and unsystematic conceptualisations of well-being pose a challenge for well-being research, as it may limit robustness, replicability, and comparability of findings across studies. Previous work has also highlighted the importance of sound well-being measurement for public policy (e.g. see Ref [33, 34]. Promoting population well-being is a Sustainable Development Goal [35], and evaluating developments in well-being, for instance in response to public policies, requires comprehensive measuring of the construct.

Well-being and life satisfaction are influenced by genetics to a moderate extent, with heritability estimates in the range of 30–40%, which leaves 60–70% of variance in well-being accounted for by environmental influences [36, 37]. A few studies have examined genetic and environmental effects on latent well-being factors and reported higher heritability estimates, such as 48% for a 'well-being factor' comprising multiple subfactors [20] and 72% for 'mental well-being' comprising emotional, social, and psychological well-being [38]. The genetic correlation (i.e. the genetic overlap) across well-being aspects may also be substantial [20, 39–41].

However, few studies have investigated the genetic and environmental architecture of general well-being factors and used items measuring multiple well-being dimensions. Gaining a better understanding of influences on well-being factors could have implications for current understanding of well-being and future studies, such as genomic studies aiming to identify specific genetic variants associated with well-being.

In the current study, we seek to advance knowledge on the structure of well-being using three large samples. The items cover several dimensions, including hedonic, eudaimonic, and social aspects of well-being. Our primary aims are threefold:

1. In Study 1, examine the hierarchical structure of well-being in a large, population-based sample of Norwegian adults ($N = 17{,}417$).
2. In Study 2, test the fit of the model identified in Study 1 in an independent sample of Norwegian adults ($N = 2125$).
3. In Study 3, estimate genetic and environmental influences on well-being factors in a population-based sample of adult twins ($N = 1987$).

Methods

Participants

We used data from three Norwegian studies. The sample size comprised 21,529 individuals in total.

Quality of life survey 2020

The nationwide Quality of Life Survey 2020 (QoL 2020) was conducted by Statistics Norway in March 2020. A random sample of 40,000 individuals was invited to participate and 17,417 responded (44%). In total, 10% of participants were aged 18–24 years, 31% were 25–44 years, 42% were 45–66 years, and 17% were 67 years and older. 51% of participants identified as female.

Quality of life survey in Hallingdal 2019

The Quality of Life Survey in Hallingdal 2019 (QoL 2019) was conducted by Statistics Norway in Hallingdal in Norway. A sample of 4000 adults was invited to participate and 2125 responded (53%). Data collection was conducted in March and April 2019. The sample was drawn randomly but stratified based on population size within the six individual municipalities. In total, 9% of participants were aged 18–24 years, 29% were 25–44 years, 45% were 45 to 66 years, and 17% were 67 years or older. 53% of participants identified as female.

The Norwegian twin registry sample

The Norwegian Twin Registry comprises several population-based twin panels [42]. We used data from 1987 twins born between 1945 and 1960 who participated in a survey in 2016 (response rate: 64%). The data comprised responses from 528 monozygotic (MZ) female twins, 627 dizygotic (DZ) female twins, 375 MZ male twins, and 457 DZ male twins. In total, data were collected from 708 complete same-sexed twin pairs (i.e. 1416 individuals) and 571 single responders. Zygosity was determined by a questionnaire which has previously been shown to be highly accurate (> 97% correct classifications) [43]. The mean age was 63 years ($SD = 4.5$). 72% were aged 45 to 66 years and 28% were 67 years or older.

Measures of well-being

We report the 37 items included in Study 1 (EFA) and Study 2 (CFA) in Table 1 (items in Study 3 are reported in the Supplementary Materials). Items originated from several well-established scales, including the Satisfaction with Life Scale [44], The Warwick–Edinburgh Mental Well-being Scale [45], The Mastery Scale [46], The Flourishing Scale [47], and international evaluations of well-being [48, 49].

Data analysis

All analyses were conducted in the R Statistical Environment [50].

Study 1: exploratory factor analysis in the quality of life survey 2020

We conducted an EFA following a general approach outlined by Watkins [51]. Factor retention was based on three empirical criteria: Scree test, parallel analysis, and the minimum average partial (MAP) method. Scree tests plot eigenvalues from the correlation matrix to assess the location of any major drops in the graph [52]. Factors extracted after major drops are assumed to mostly represent error variance and are therefore not retained [51]. Parallel analysis compares observed and simulated eigenvalues (based on random data with an equal number of variables and sample size), retaining factors for which observed eigenvalues exceed simulated ones [53]. MAP separates common and unique variance in factor extraction: the lowest value is indicative of the point where all common variance is removed [51, 54]. The correlation matrix was estimated using Spearman correlation (MAP and parallel analysis were repeated using Pearson correlation to ensure robustness).

Squared multiple correlations were used in initial communality estimates. We used the weighted least squares solution for parallel analysis and factor extraction, considering the ordinal nature of the data, and the oblique promax factor rotation method to allow for intercorrelated factors. Factor extraction was repeated using Maximum Likelihood (ML) and ordinary least squares estimation and factor rotation using oblimin, to ensure the robustness of the factor structure. Missing data were treated with pairwise deletion.

We subjected the factor intercorrelation matrix to a new EFA, which can be done in hierarchical factor analysis [51], using the same empirical criteria. In addition, we examined the higher-order factor structure using the Schmid–Leiman transformation. EFA was conducted using the *psych* package [55].

Study 2: confirmatory factor analysis in the quality of life survey in Hallingdal 2019

Following the EFA, we examined the fit of the factor model identified in Study 1 in an independent sample. We used the diagonally weighted least squares estimator (DWLS), as this outperforms ML for ordinal data [56]. Missing data were treated with listwise deletion. The CFA suffered from some data loss (813 observations), as two relationship satisfaction items were asked a subset of the sample only (participants with a partner and/or children). We examined model fit both with and without these items.

Model fit was assessed using several fit indices, including the Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), root mean square error of approximation (RMSEA), and Standardised Root Mean Square Residual (SRMR). Good model fit was determined by conventional thresholds [57]: CFI > 0.95, TLI > 0.95, RMSEA < .06, and SRMR < .08. The CFA was conducted using the *lavaan* [58] and *semPlot* [59] packages.

Table 1 Well-being items included in the EFA and CFA

Item no	Question text	Scale or single item
Q1	In most ways my life is close to my ideal	SWLS[a]
Q2	The conditions of my life are excellent	SWLS[a]
Q3	I am satisfied with life	SWLS[a]
Q4	So far I have gotten the important things I want in life	SWLS[a]
Q5	If I could live my life over, I would change almost nothing	SWLS[a]
Q6	How often do you experience being interested in what you are doing?	ESS[b]
Q7	How often do you experience being absorbed in what you are doing?	ESS[b]
Q8	How often do you experience being enthusiastic about what you are doing?	ESS[b]
Q9	I've been feeling optimistic about the future	WEMWBS[c]
Q10	I've been feeling useful	WEMWBS[c]
Q11	I've been feeling relaxed	WEMWBS[c]
Q12	I've been dealing with problems well	WEMWBS[c]
Q13	I've been thinking clearly	WEMWBS[c]
Q14	I've been feeling close to other people	WEMWBS[c]
Q15	I've been able to make up my own mind about things	WEMWBS[c]
Q16	I have little control over what happens to me	Mastery scale[d]
Q17	Some of my problems I simply cannot solve	Mastery scale[d]
Q18	There is little I can do to change aspects of my life that are important	Mastery scale[d]
Q19	When faced with problems in my life I often feel helpless	Mastery scale[d]
Q20	Sometimes it feels like I am only pushed around in life	Mastery scale[d]
Q21	Overall, how satisfied are you with your life at the moment?	OECD[e,g]
Q22	Overall, to what extent do you experience what you're doing in life as worthwhile?	OECD[e,g]
Q23	In the last 7 days, to what extent have you been happy?	Adapted from OECD[e,g]
Q24	In the last 7 days, to what extent have you been worried?	Adapted from OECD[e,g]
Q25	In the last 7 days, to what extent have you been feeling down or sad?	Adapted from OECD[e,g]
Q26	My social relations are supportive and rewarding	Flourishing scale[f]
Q27	I actively contribute to the happiness and well-being of others	Flourishing scale[f]
Q28	Do you think your life is mostly full of experiences and rich, or mostly empty and boring?	Single item[g]
Q29	Overall, how happy with your life do you think you will be in 5 years?[h]	Single item[g]
Q30	In the last 7 days, to what extent have you been irritated?	Single item[g]
Q31	In the last 7 days, to what extent have you been invested/engaged?	Single item[g]
Q32	In the last 7 days, to what extent have you been calm and relaxed?	Single item[g]
Q33	In the last 7 days, to what extent have you been anxious?	Single item[g]
Q34	In the last 7 days, to what extent have you been stressed?	Single item[g]
Q35	How happy are you with your relationship with your children?	Single item[g]
Q36	How happy are you with your relationship with your friends?	Single item[g]
Q37	How happy are you with your relationship with your partner?	Single item[g]

[a]Satisfaction with Life Scale [44]

[b]European Social Survey (2013)

[c]The Warwick–Edinburgh Mental Well-being Scale [45]

[d]The Mastery Scale [46]

[e]OECD (2013)

[f]The Flourishing Scale [47]

[g]These items have been recommended for national monitoring of well-being in the Norwegian population (Nes et al., 2018)

[h]This item was not a part of the QoL 2020 survey and therefore only included in the EFA

Study 3: examining genetic and environmental influences on well-being factors in the Norwegian twin registry (1945–1960 cohort)

In Study 3, we first conducted a CFA to test the fit of a hierarchical factor model with multiple first-order factors and a higher-order factor. This CFA used the DWLS estimator and model fit was assessed using similar fit indices as in Study 2. This analysis examined the fit of a model which was broadly similar to the model in Studies 1 and 2 in terms of including first-order factors and a higher-order factor, but the factors comprised partially different items. Optimism was included as a separate component, as it was measured by multiple items. Meaning in life was included as a distinct component, as the inclusion of this item in the "life satisfaction" component led to unreasonable parameter estimates with one communality estimate larger than 1.00 (i.e. a Heywood case). Three items measuring positive affect in daily life comprised a factor we called 'positive affect', as opposed to 'positive activation'.

We examined genetic and environmental influences on the general well-being factors using biometric modelling [60, 61]. In this approach, phenotypic variation is explained by the influences of four components: additive genetic effects (A; correlated 1.0 for MZ twins and .5 for DZ twins), non-additive genetic effects (D; correlated 1.0 for MZ twins and .25 for DZ twins), shared environmental effects (C; correlated 1.0 for both MZ and DZ twins), and non-shared environmental effects (E; uncorrelated for both MZ and DZ twins).

Participants received an index score for each well-being factor based on the items which loaded on the given factor in the CFA in Study 3, if they had responded to more than half of the items in the index. Biometric analyses were conducted using mean scores on these indices as outcome variables. Individual item responses were standardised prior to computing index scores.

Correlational analyses were conducted to assess similarity in index scores across twins. Genetic and environmental influences on well-being components were examined using two multivariate models. The Cholesky model decomposes covariance between the latent A, C, and E variables and allows for estimating genetic and environmental correlations [62]. Multiple Cholesky models were estimated and compared for model fit, including models with A, D, and E effects (ADE); A, C, and E effects (ACE); A and E effects (AE); C and E effects (CE); and E effects only (E). The full ADCE model requires data from additional familial relationships and was therefore not estimated. Finally, we estimated a Common Pathway (CP) model, which assumes that covariation between index scores is explained by a latent well-being factor. The data were residualised on age and sex prior to conducting analyses. Biometric analyses were conducted using the *umx* [63] and *OpenMx* [64] packages.

Results

Study 1: exploratory factor analysis in the quality of life survey 2020

Initial analyses indicated that conducting EFA was appropriate. Most item correlations exceeded 0.30 and none exceeded 0.90 (see Supplementary Materials). Based on Bartlett's [65] test of sphericity, the hypothesis that the correlation matrix was an identity matrix was rejected ($x^2 = 414635.90, DF = 666$). The Kaiser–Meyer–Olkin [66] measure of sampling adequacy was acceptable. The overall value was .97 and values for the measured variables ranged from .94 to 99.

Empirical criteria suggested to retain from 6 (MAP) to 10 (parallel analysis) factors. Factor structures retaining from 6 to 10 factors were assessed for interpretability, meaningfulness, and symptoms of over- or underextraction. The most interpretable solution retained six factors. We called the first factor 'life satisfaction', as it comprised items assessing life satisfaction, experiencing life as meaningful, and optimism (Q21, Q22, Q28, Q29, Q1–Q5). The second factor, 'positive activation', comprised items assessing experiences of being engaged in and enthusiastic about one's activities (Q6–Q8, Q31). Items loading on the third component, 'autonomy', queried about self-perceived (lack of) control over what happens in life, ability to find solutions, and feelings of hopelessness (Q16–Q20). The fourth factor, 'well-functioning', comprised several 'functional' aspects of well-being (e.g. cognition, problem-solving). It included items asking about recently having felt optimistic, been able to deal with problems well, been thinking clearly, and having felt close to other people (Q9–Q15). The fifth factor, 'social', included items assessing aspects of social relationships (Q26, Q27, Q35–Q37). Items loading on the final component, 'absence of negative affect', primarily assessed recently experienced negative affect (Q23–Q25, Q30, Q32–Q34). Standardised factor loadings are reported in Table 2 (empirical criteria and robustness analyses are reported in the Supplementary Materials).

Several variables had complex cross-loadings. Q22, Q28, and Q29 loaded on both the life satisfaction and positive activation factors; Q9 loaded on both the well-functioning and life satisfaction factors; Q10 loaded on both the well-functioning and positive activation factors; Q11 loaded on both the well-functioning and absence of negative affect factors; Q14 loaded on both the well-functioning and the social factors; Q23 loaded on the absence of negative affect, positive activation, social, and life satisfaction factors; Q31 loaded on both the positive activation and well-functioning factors; and

Table 2 Factor loadings > .20 for six-factor solution with promax rotation (pattern matrix)

Item no	Description	LS	Standardised loadings					
			PA	AUT	WF	SOC	ANA	Communality[a]
Q1	Life close to ideal	**.99**						.75
Q3	Life satisfaction	**.96**						.79
Q4	Important things in life	**.87**						.56
Q2	Life conditions excellent	**.83**						.59
Q5	Change nothing	**.74**						.48
Q21	Overall life satisfaction	**.63**						.66
Q28	Life full of experiences and rich	**.49**	**.35**					.68
Q22	Life is worthwhile	**.47**	**.40**					.63
Q29	Happy with life in 5 years	**.39**	**.31**					.53
Q8	Enthusiastic		**1.01**					.77
Q7	Absorbed		**1.00**					.70
Q6	Interested		**.89**					.73
Q31	Last 7 days, invested/engaged		**.56**		.22			.52
Q18	Unable to change aspects of life			**.85**				.57
Q17	Cannot solve problems			**.79**				.51
Q16	Little control over what happens			**.65**				.42
Q19	Helpless when faced with problems			**.64**				.60
Q20	Pushed around in life			**.43**				.49
Q13	Thinking clearly				**.89**			.62
Q12	Dealing with problems well				**.73**			.61
Q15	Able to make up my own mind				**.63**			.39
Q14	Feeling close to other people				**.46**	**.37**		.50
Q11	Feeling relaxed				**.42**		**.35**	.52
Q10	Feeling useful		.26		**.42**			.53
Q9	Feeling optimistic about the future	.26			**.26**			.48
Q26	Supportive and rewarding relations					**.77**		.60
Q36	Happy with relationship with friends					**.66**		.47
Q27	Contribute to happiness of others					**.64**		.51
Q35	Happy with relationship with children					**.63**		.33
Q37	Happy with relationship with partner					**.62**		.40
Q24	Last 7 days, worried						**.86**	.62
Q33	Last 7 days, anxious						**.84**	.63
Q34	Last 7 days, stressed						**.80**	.55
Q25	Last 7 days, down or sad						**.73**	.67
Q30	Last 7 days, irritated						**.56**	.37
Q32	Last 7 days, calm and relaxed				.24		**.43**	.51
Q23	Last 7 days, happy	.20	.21			.21	**.27**	.61

[a]Communality is the proportion of variance explained by the factors [51]. LS represents 'life satisfaction'; PA represents 'positive activation'; AUT represents 'autonomy'; WF represents 'well-functioning'; SOC represents 'social'; and ANA represents 'absence of negative affect'. Loadings > .20 are displayed and loadings > .30 are in bold. Item descriptions are based on the full items, as reported in Table 1. The loadings from the pattern matrix reflect regression-like coefficients and may exceed ± 1 [51]. The EFA was conducted in the QoL 2020 sample

Q32 loaded on both the absence of negative affect and well-functioning factors.

All criteria suggested that one higher-order factor could be extracted. We called this 'the general happiness factor' (the 'h-factor'). With one exception, all first-order factors had loadings > .70 on this higher-order factor. The standardised loadings to the higher-order factor were .89 for life satisfaction, .82 for positive activation, .67 for autonomy, .83 for well-functioning, .75 for social, and .72 for absence of negative affect.

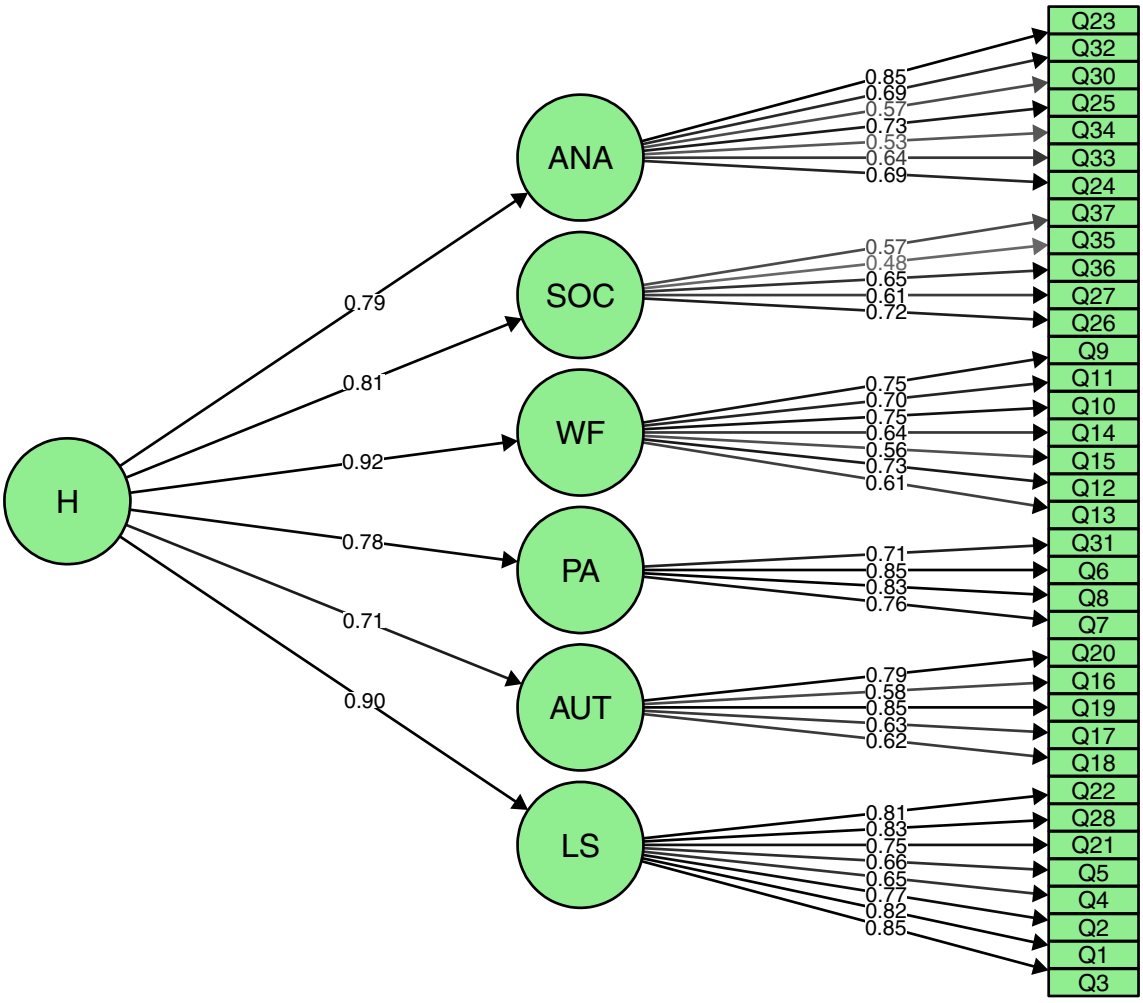

Fig. 1 CFA Results of Model with Six First-Order Factors and One Higher-Order Factor. *ANA* absence of negative affect; *SOC* social; *WF* well-functioning; *PA* positive activation; *AUT* autonomy; and *LS* life satisfaction. The plot depicts the standardised factor loadings. The CFA was conducted in the QoL 2019 sample

Study 2: confirmatory factor analysis in the quality of life survey in Hallingdal 2019

In Study 2, we examined the fit of the factor model identified in Study 1 in an independent sample. The factor structure was pre-defined to be identical with the structure identified in Study 1: individual items loaded on one of six well-being factors, which all loaded on a single higher-order factor. All statistics indicated good model fit: $\chi^2 = 1528.732(df = 588, p < .001)$, RMSEA = .035 (90%CI:.033, .037), SRMR = .053, CFI = .987 and TLI = .986. (see Fig. 1).

Study 3: biometric modelling in the Norwegian twin registry sample

All model fit statistics indicated that the model with a higher-order and multiple first-order factors was a good fit to the data: $\chi^2 = 1313.827(df = 489, p < .001)$, RMSEA = .035 (90%CI:.033, .038), SRMR = .053, CFI = .976 and TLI = .974.

Table 3 Twin correlations for index scores

Index mean score	Monozygotic		Dizygotic	
	Twin 1	Twin 2	Twin 1	Twin 2
Life Satisfaction twin 1	1.00	.252	1.00	.146
Meaning twin 1	1.00	.283	1.00	.150
Optimism twin 1	1.00	.337	1.00	.233
Absence of negative affect twin 1	1.00	.382	1.00	.132
Positive affect twin 1	1.00	.242	1.00	.126
Autonomy twin 1	1.00	.336	1.00	.081
Social twin 1	1.00	.387	1.00	.104

Table 4 Fit statistics for multivariate twin models

Model	df	Δ Fit	Δ df	p	AIC	Δ AIC	RMSEA [95% CI]
Multivariate cholesky (ACE)	91				27,870.19	–	.020 [.013, .026]
Multivariate cholesky (ADE)	91	− 12.512	0		27,857.68	− 12.512	.018 [.011, .025]
Multivariate cholesky (AE)	**63**	**3.951**	**28**	**1.000**	**27,818.14**	**− 52.049**	.015 [.007, .021]
Multivariate cholesky (CE)	63	49.760	28	.007	27,863.95	− 6.240	.021 [.015, .026]
Multivariate cholesky (E)	35	230.124	56	< .001	27,988.31	118.124	.031 [.026, .036]

The model fit statistics for the best-fitting model indicated by RMSEA and AIC values are in bold

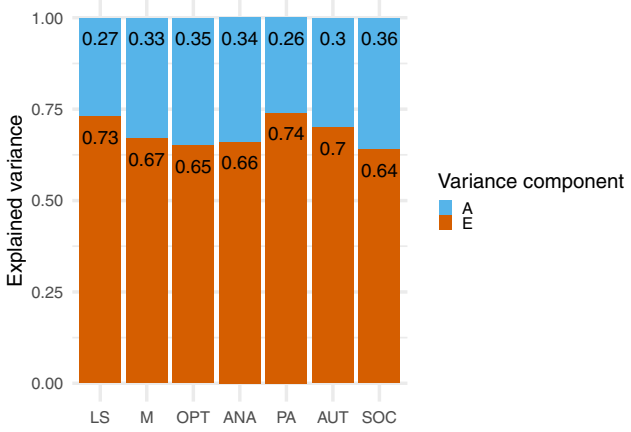

Fig. 2 Estimated Genetic and Environmental Effects on Well-being Components. 'A' represents additive genetic effects and 'E' represents non-shared environmental effects. 'LS' represents life satisfaction; 'M' represents meaning in life; 'OPT' represents optimism; 'ANA' represents absence of negative affect, 'PA' represents positive affect; 'AUT' represents autonomy; 'SOC' represents Social. We report confidence intervals for the A and E variance components in the Supplementary Materials

Index score correlations were systematically higher for MZ than DZ co-twins, indicative of genetic influence on all well-being factors (see Table 3). The AE Cholesky model had best fit to the data, indicated both by AIC and RMSEA values (see Table 4). Moderate genetic influence and substantial non-shared environmental influence was observed for all first-order well-being factors, with heritability estimates ranging from .26 to .36 (see Fig. 2; parameter estimates, confidence intervals, and genetic and environmental correlations are reported in the Supplementary Materials).

The AE CP model had worse fit compared with the AE Cholesky model ($AIC = 28001.840; RMSEA = .032, 95\% CI[.027, .036]$). The heritability of the latent well-being factor estimated in the AE CP model was 40% (see Fig. 3).

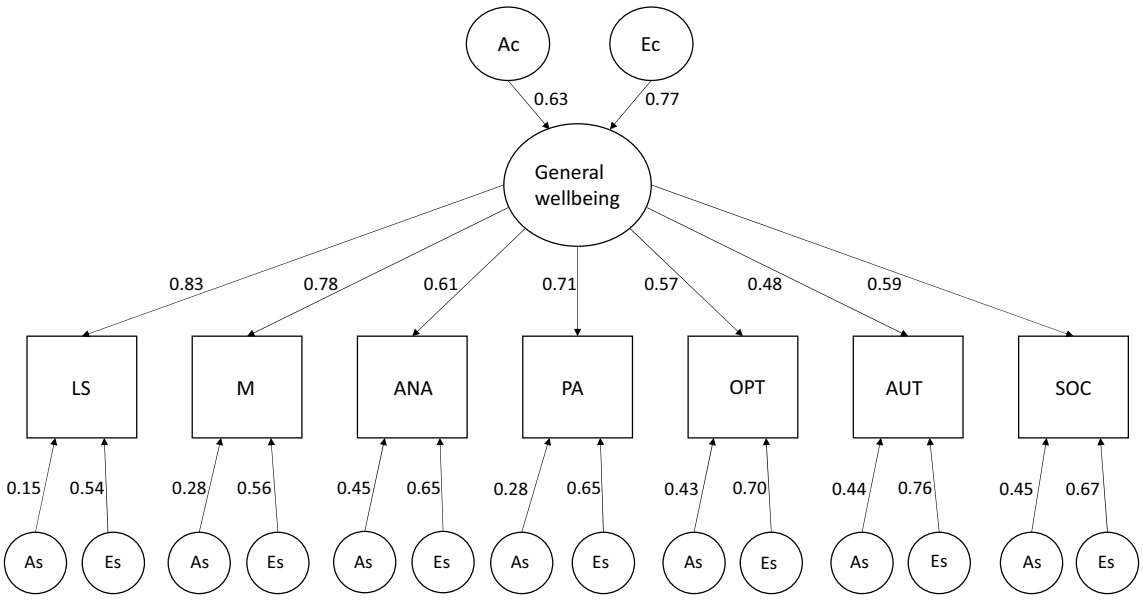

Fig. 3 Parameter Estimates from Common Pathway Model. We note that this model had worse fit compared with an AE Cholesky model but good fit indicated by RMSEA

Discussion

Across more than 21,500 participants, we identified a well-being structure comprising six first-order factors and one higher-order factor. This model had excellent fit in an independent sample. All well-being factors, including the higher-order happiness factor, showed moderate genetic and substantial non-shared environmental influence.

Our results suggest that the structure of well-being encompasses both hedonic and eudaimonic aspects, which were subsumed in broader factors. The factor model included both well-being facets conceptualised as 'hedonic' [7], like the presence of positive and absence of negative affect, and aspects classified as 'eudaimonic' [9], such as well-functioning. In addition, social aspects of well-being, emphasised in recent models [11], comprised a first-order factor with a strong loading on the higher-order factor. One previous study found that a best-fitting hierarchical model comprised hedonic, eudaimonic, and social higher-order factors [4].

Our finding of six first-order well-being components is in partial agreement with previous studies which have also identified multiple general well-being factors [4, 15–17, 19–22, 30, 67–72]. Specific well-being components identified across studies are likely to vary, in part because well-being may be measured using different items and scales [69], which should be kept in mind when interpreting our findings. Furthermore, some items loaded on more than one factor in our EFA. We note, however, that global fit statistics from the subsequent CFA indicated good model fit.

All first-order factors loaded strongly on a higher-order well-being factor (the h-factor). This corroborates findings from several studies which have found evidence for a general higher-order factor in hierarchical or bifactor models of well-being [4, 19–22, 26, 27, 30, 67]. The hierarchical model can be interpreted as nested within the bifactor model [51, 73, 74]. Thus, our findings support converging evidence, from studies applying both hierarchical and bifactor models, in identifying one general well-being factor. We note that random measurement error is typically contained at the item level and not present in the higher-order latent factor.

We note that these well-being factors refer to statistical constructs. Theoretical work is needed to better understand what the higher-order well-being factor reflects. One possibility is that it broadly corresponds with 'overall perceived enjoyment and fulfilment with life', as proposed by Disabato et al. [18]. A similar higher-order factor has also been theorised to represent a 'positive orientation' towards life [40, 75], with one study indicating that positive orientation may reflect a common factor for hedonic and eudaimonic well-being [76]. However, interpreting the general factor is difficult given the multidimensional nature of well-being, and some have noted that the single factor may not actually reflect a positive construct [23].

Our study yields novel findings regarding the genetic and environmental architecture of well-being. All first-order well-being factors showed moderate genetic and substantial non-shared environmental influence. Several heritability estimates are close to previously reported estimates, e.g. we estimate the heritability of life satisfaction to be 27%, compared with 32% in one previous meta-analysis [36]. Heterogeneity in well-being measures likely contributes to variation heritability estimates across studies [36], together with other factors, such as measurement error. Age differences could also be a contributing factor to varying heritability estimates across studies and samples. However, Bartels [36] did not find a substantial effect of age on heritability estimates.

The higher-order factor had a heritability estimated to 40% (in the Common Pathway model), which is close to what has been reported for well-being (36%) and somewhat higher than for life satisfaction (32%) [36]. This estimate is lower than what has been reported for a latent 'Well-being' factor (48%) [20] and latent 'mental well-being' factor (72%) [38].

Strengths and limitations

Our study has several strengths. We used three large and independent samples to examine the structure of well-being, two of which were population based. Well-being was measured using multiple items from several questionnaires with different well-being conceptualisations. Thirdly, we used both EFA and CFA to examine the factor structure of well-being and its replicability, leveraging both exploratory and confirmatory factor analytic approaches.

Our study also has several limitations. First, although well-being components were broadly corresponding across studies, the factor structure was modelled with minor differences in the twin sample due to partially different items. However, this model also had good fit to the data, providing further support for a hierarchical well-being model. Second, data were residualised on sex but possible sex differences in genetic and environmental effects were not investigated. Findings have been inconclusive with regards to sex differences in these effects on well-being [36]. Third, our samples consisted only of Norwegian adults. Aspects of well-being which are emphasised vary across cultures [77], leaving the generalisability of the identified well-being structure in our study unclear. Fourth, a theoretical framework for explaining the structure of well-being we identify is lacking. There have been calls for more emphasis on theoretical work alongside factor analysis [78] and in well-being research [79].

Fifth, previous studies have tested the external validity of bifactor models for the p-factor [80]. Our study is limited in that it does not evaluate the external validity of the factor models. Sixth, data collection for QoL 2020 was conducted during the first national lockdown in Norway related to the Coronavirus Disease 2019 pandemic, possibly influencing responses. We note that model identified using EFA had excellent fit in the QoL 2019 survey data, collected before the pandemic outbreak.

Implications

Our findings have implications for understanding the structure of well-being. Firstly, hedonic and eudaimonic well-being were not distinguishable as distinct components but included in broader factors. Thus, models which conceptualise these as separate components may not accurately capture the structure of well-being. Secondly, we identified a higher-order happiness factor, which underlies the structure of well-being. Thirdly, genetic effects on well-being factors, including the higher-order factor, were moderate, with the majority of variance explained by non-shared environmental factors.

Our findings may have multiple implications for future research. Examining the content of the higher-order happiness factor, its correlates, and the structure of genetic and environmental influences on this factor could be a useful aim for future studies. Furthermore, examining general well-being factors in non-Scandinavian cultures is desirable to better understand generalisability and cultural influences on well-being. Future research efforts could use longitudinal data to investigate stability and change in general well-being factors. One previous study found a high degree of stability in a latent well-being factor across six years [71].

Conclusion

We conducted three studies to advance knowledge on the structure of well-being and its genetic and environmental architecture. We identified six first-order well-being factors which all loaded on a higher-order well-being factor. The model had excellent fit in an independent sample. All well-being components were moderately influenced by genes and substantially influenced by non-shared environmental factors. Our findings have implications for understanding the structure of well-being, theories of well-being, and future research efforts.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11136-023-03437-7.

Acknowledgements We would like to thank the participants of the QoL 2019 and QoL 2020 surveys, and the participants from the Norwegian Institute of Public Health Twin Panel.

Author contributions All authors contributed to the study conception and design. Data analysis was conducted by LDB. The first draft of the manuscript was written by LDB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Open access funding provided by University of Oslo (incl Oslo University Hospital). We acknowledge funding from the Research Council of Norway (Grant Nos. 314843; 288083). NOC was also supported by grant 326350 from the Research Council of Norway.

Declarations

Conflicts of interest None.

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II

Mental health and environmental factors in adults: A population-based network analysis

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Abstract

Few studies have assessed the multifactorial nature of environmental influences on population mental health. In this large-scale, population-based study of adults, we applied network analysis to study the relationship between environmental factors and symptoms of depression, anxiety, and wellbeing. We estimated networks with overall mental health nodes and individual symptoms to assess both broad- and fine-grained associations between environmental factors and mental health. Finally, we conducted an out-of-sample replication in an independent large-scale sample to assess the robustness of our results. Across 31,000 adults randomly sampled from the Norwegian population, we identified associations between numerous environmental characteristics and mental health. Recent discrimination and unsupportive social environments were strongly associated with lower population wellbeing and higher levels of mental illness symptoms, respectively. The most strongly connected variables in the networks were environmental factors, including perceived problems with crime, violence, or vandalism in the residential area, worrying about violence or threats when outside, and problems with noise or contamination at home. Substantial variation in population mental health was explained by environmental factors included in the networks. Replicability of the results was excellent and suggestive of strong robustness of the results across samples. Our findings are indicative of the importance of environmental factors, such as the social environment, housing satisfaction, and residential area characteristics, for multiple aspects of population mental health. We identify several environmental factors which represent potentially useful targets for future studies and public health efforts seeking to improve mental health in the general population.

Introduction

Symptoms of anxiety and depression have high prevalence in the general population and represent a considerable burden to societies worldwide (GBD 2019 Diseases and Injuries Collaborators, 2020). The prolonged constellation and long-term stability of such symptoms may emerge into mental health disorders (e.g., Ebrahimi et al., 2021), and while efficacious treatments are available, many individuals do not respond to current treatments (Barth et al., 2016; Cipriani et al., 2009). The reduction in disease burden due to treatment (assuming optimal treatment conditions) of common mental health disorders has been estimated to 40%, indicating that current treatments do not adequately alleviate this disease burden (Andrews et al., 2004; Holmes et al., 2018). Furthermore, in the Norwegian population, a minority of individuals with common mental illnesses have been in contact with health care providers, highlighting a gap between needed and received treatment (Folkehelseinstituttet, 2018). Depressive symptoms below diagnosis threshold are also associated with significant reductions in health (Ayuso-Mateos et al., 2010).

In response, there have been calls highlighting the importance of efforts to prevent depression and anxiety in the population (Bienvenu & Ginsburg, 2007; Cuijpers et al., 2012). However, the comprehensive implementation of prevention strategies which target common population mental health problems such as depression has not yet been accomplished (Cuijpers et al., 2012), and advancing prevention efforts represents a 'grand challenge' in global mental health (Collins et al., 2011). It is now widely acknowledged that mental health is not merely the absence of mental illness but also comprises wellbeing (World Health Organization, 2004), and promoting population wellbeing is a Sustainable Development Goal for member states of the United Nations (United Nations General Assembly, 2015). Wellbeing predicts physical health and longevity (Diener & Chan, 2011), improvement in positive mental health is associated with lower risk of mental illness (Keyes et al., 2010), and

better mental health is associated with greater psychosocial functioning and less work absence (Keyes, 2007). Thus, identifying factors related to wellbeing and adverse mental health is of importance to public health efforts worldwide.

While individual factors such as genetics are associated with increased risk of psychopathology symptoms (Czajkowski et al., 2010), numerous environmental factors are also related to anxiety and depressive symptoms in the population. For instance, quality of housing has been associated with depressive symptoms in multiple studies (Rautio et al., 2017; Shah et al., 2018), and noise annoyance and traffic noise have been linked to anxiety and depressive symptoms in both prospective and cross-sectional studies (Beutel et al., 2020; Generaal et al., 2019). Air pollution was associated with increased risk of common mental disorders in a recent longitudinal study (Bakolis et al., 2021). Conversely, more neighbourhood greenspace has been related to lower depressive symptoms (Beyer et al., 2014; South et al., 2018). Social cohesion and safety have been associated with higher prevalence of anxiety and depressive disorders and increased symptom levels in community and health care settings (Generaal et al., 2019). Thus, both characteristics related to the physical and social environment are associated with community and population mental health.

Multiple environmental characteristics are also associated with wellbeing, such as spending more time in green and natural habitats (MacKerron & Mourato, 2013; Tost et al., 2019), neighbourhood safety (van de Weijer et al., 2022), and air pollution (Welsch, 2006). Crime levels and fear of crime in the immediate living environment have been found to be theoretically and empirically related to wellbeing (Lorenc et al., 2012). Higher wellbeing has also been associated with greater perceived social cohesion (Delhey & Dragolov, 2016; Williams et al., 2020) and satisfaction with democratic governance and politics (Orviska et al., 2014) in cross-sectional studies. Thus, several environmental characteristics are also related to population wellbeing.

While a number of environmental factors associated with mental health have been identified, knowledge is lacking regarding how such factors influence mental health (van der Wal et al., 2021). The nature of these relationships is likely multifactorial, involving complex associations between environmental factors and mental health, as well as interactions between environmental factors themselves. Accordingly, it has been argued that a systems-based approach is needed to understand relationships between environmental factors and population health outcomes, in particular in urban areas (Glouberman et al., 2006; Rydin et al., 2012). The emergence of systems-based approaches in clinical psychology (Borsboom et al., 2021) has highlighted the importance of understanding how phenomena, such as adverse mental health states (Borsboom, 2017), arise from patterns of interaction and self-reinforcing feedback loops among their constituent elements. This shifts the focus toward examining associations between these elements to better understand their interplay and how vulnerabilities can combine to produce adverse mental health symptoms and reduced wellbeing. The realization of this systems-based perspective has been facilitated by network analytic techniques, which seek to delineate fine-grained relationships between psychological and contextual processes that may exacerbate symptomatology and undermine resilience (Borsboom et al., 2021; Borsboom & Cramer, 2013). The value of applying systems-based approaches in public health research has also been underscored elsewhere (Luke & Stamatakis, 2012; Rutter et al., 2017; Rydin et al., 2012). A systems-based approach could yield new insights into how environmental factors are related to population mental health and how different factors interact to increase the risk of adverse mental health symptoms and reduced wellbeing.

Network analysis typically focuses on identifying important components of a network (nodes) and relationships between the different components (edges). These estimated conditional associations are visualized through network plots, highlighting unique

relationships between the nodes after controlling for all other nodes in the network (Borsboom et al., 2021). This can give insights into complex relationships between a set of nodes in a network.

Although few network studies have examined associations between environmental characteristics and population mental health, recent studies have investigated how genetic and environmental factors (such as adversity) are related to psychopathology symptoms (Garcia-Mondragon et al., 2022; Steen et al., 2021; van Loo et al., 2018). One 2019 study found that factors such as neighbourhood social cohesion and disorder were associated with anxiety symptoms and that environmental factors were also strongly connected to each other (McElroy et al., 2019). In a network study of environmental factors and wellbeing, McElroy et al. (2021) found that wellbeing was associated with multiple factors, such as using local greenspaces and experiencing neighbourhood cohesion. Notably, McElroy et al. (2021) also identified fine-grained associations between specific environmental characteristics and wellbeing aspects, e.g., greenspace use was associated with feeling useful and feeling close to other people. Thus, this suggests that environmental factors are associated with broad mental health constructs and may also show distinct connections to specific aspects of mental health.

In the current study, we apply network analysis to advance current understanding of the relationships between mental health and environmental factors in several ways. First, knowledge on the multifactorial relationships between mental health and environmental characteristics is scarce (van der Wal et al., 2021). Network analytic studies can delineate the most important components in this relationship through simultaneous testing of putative factors and statistically controlling for their associations with each other. The present study was exploratory in nature, aiming to shed light on multifactorial connections between environmental characteristics and mental health. Second, few studies have examined if environmental characteristics are differently related to distinct aspects of population mental

health, such as mental illness symptoms and wellbeing. Third, few studies have assessed associations between environmental characteristics and broad mental health constructs *and* granular associations between environmental factors and specific aspects of population mental health (e.g., individual depressive symptoms). Finally, few studies have tested the replicability of estimated networks in independent samples, which can yield insights into the generalisability of networks and serve as a test of their robustness (Borsboom et al., 2021).

We had three aims in the current study:

1. Identify the most important nodes and edges in separately estimated networks with environmental characteristics and an overall wellbeing node, an overall depressive node, and an overall anxiety node;
2. Examine fine-grained associations between environmental characteristics and specific wellbeing aspects, depressive symptoms, and anxiety symptoms;
3. Conduct out-of-sample replications of all networks in an independent large-scale population-based sample of the target population to estimate the robustness and replicability of the findings.

Methods

Key sample characteristics are provided in Table 1.

Table 1

Demographic Characteristics of the Samples

Characteristics	QoL 2021 (Main sample) Number of respondents (%)	QoL 2020 (Replication sample) Number of respondents (%)
Gender[a]		
Female	9038 (51.73)	8914 (51.19)
Male	8360 (47.85)	8430 (48.41)
Other	75 (.43)	68 (.39)
Age group		
18-24	1607 (9.19)	1798 (10.32)
25-44	5418 (30.98)	5443 (31.25)
45-66	7374 (42.17)	7238 (41.56)
67-79	2670 (15.27)	2545 (14.61)
> 79	418 (2.39)	393 (2.26)
Marital status[b]		
Married or registered partner	8470 (48.48)	8385 (48.20)
Cohabiting	3618 (20.71)	3608 (20.74)
Not married or cohabiting	5384 (30.82)	5405 (31.07)
Education level[c]		
Unknown or no education	409 (2.34)	481 (2.76)
No higher education	9163 (52.40)	9619 (55.23)
Higher education (university or college)	7915 (45.26)	7317 (42.01)
Living in an urban setting[d]	14440 (83.13)	14293 (82.67)
Sexual orientation[e]		
Heterosexual	16360 (94.20)	16363 (94.47)
Other	1008 (5.80)	957 (5.53)

Notes. [a]14 respondents did not wish to answer or answered 'Don't know' for this item in the QoL 2021 survey; 5 in QoL 2020. [b]15 respondents did not wish to answer or answered 'Don't know' for this item in the QoL 2021 survey; 19 in QoL 2020. [c]Data was missing for this variable for 154 respondents in the QoL 2021 survey; 147 in QoL 2020. [d]Data was missing for this variable for 116 respondents in the QoL 2021 survey; 127 in QoL 2020. [e]119 respondents did not wish to answer or answered 'Don't know' for this item in the QoL 2021 survey; 97 in QoL 2020.

Samples

Quality of Life Survey 2021 (Main sample)

The Quality of Life Survey 2021 (QoL 2021) was conducted by Statistics Norway in 2021 (Pettersen & Støren, 2021). A nationally representative sample of 40,000 adults (18

years and older) currently living in Norway was randomly drawn from the population registry database of Statistics Norway. The response rate was 43.7% and data were collected in March 2021, resulting in a final sample size of 17,487. Data were collected using an online survey.

While the final sample is broadly representative of the Norwegian population, some respondent groups were overrepresented, including respondents with higher education, respondents belonging to the age group 45-66 years, and respondents with a Norwegian country background.

Quality of Life Survey 2020 (Replication sample)

The Quality of Life Survey 2020 (QoL 2020) was conducted by Statistics Norway in 2020 (Pettersen & Støren, 2020), and used as the replication sample in the present study. A nationally representative sample of 40,000 adults (18 years and older) currently living in Norway was randomly drawn from the population registry data base of Statistics Norway. The data were collected in March 2020 and the response rate was 43.6% and, resulting in a final sample size of 17,417. As for the QoL 2021 data, respondents with higher education, belonging to the age group 45-66 years, and with a Norwegian country background were overrepresented in the final sample. Both samples were similar in characteristics and adapted the same random sampling strategy on the same population of participants.

Measures

Wellbeing was measured using the Satisfaction with Life Scale (SWLS; Diener et al., 1985). SWLS consists of 5 items with a response format based on a 7-point Likert scale, ranging from 1 (‘Totally disagree’) to 7 (‘Totally agree’). The individual items assess the extent to which respondents agree or disagree that life is close to one’s ideal, that one’s life conditions are very good, that one is satisfied with life, that one feels they have gotten the most important things they wished in life, and if one would have changed much about life if given the chance to live again. Participants were required to respond to all items to receive a

wellbeing sum score. The item life is close to one's ideal was not included in the item-level wellbeing network because of conceptual similarity with the item life conditions are very good (a network estimated with both items is reported in the Supplementary Materials).

Anxiety and depressive symptoms (in the last 14 days) were measured using a short-form of the Symptom Checklist (SCL; Hesbacher et al., 1980; Tambs & Røysamb, 2014). Anxiety symptoms included feeling nervous or experiencing shakiness inside, experiencing sudden fear for no reason, and feeling fearful or anxious. Depressive symptoms included feeling blue, feeling hopeless about the future, worrying too much about things, and experiencing sleeping problems. Participants were required to have responded to at least 50% of the items to receive an anxiety and/or depression mean score. The minimum mean score was 1 and maximum mean score was 4 for depressive and anxiety symptoms.

Sixteen environmental characteristics were assessed and included in the networks. These included various aspects of the surrounding environment, such as perceiving the social environment as supportive, housing satisfaction, residential area problems, and having experienced recent discrimination. Perceiving social relations as supportive and rewarding was included as it describes the social *environment* surrounding an individual. Having experienced discrimination was included as this can be understood as a stressful life event which is intimately linked to the surrounding environment and/or society. All self-report items measuring environmental factors have been recommended for national monitoring of quality of life in the Norwegian population (Nes et al., 2018). We also included some environmental characteristics based on national registry data (i.e., objective). We report the individual nodes and their characteristics in Table 2. All items are reported in the Supplementary Materials. The studies conducted by Statistics Norway were approved by Statistics Norway's data protection officer. The Quality of Life data may be requested from the Norwegian Centre for Research Data (https://www.nsd.no/en/). This study was not pre-registered.

Table 2.

Characteristics of Environmental Nodes.

Environmental characteristic	Response format	Self-report or registry
Supportive and rewarding social relations	0-10 rating scale	Self-report
Satisfaction with area/village/district	0-10 rating scale	Self-report
Satisfaction with housing	0-10 rating scale	Self-report
Sense of belonging to residential area	0-10 rating scale	Self-report
Household crowding (number of people in household divided by number of rooms)[a]	—	Registry-data
Feeling safe when out walking in the local environment	0-10 rating scale	Self-report
Trust in help from the public sector if becoming ill, injured or unable to work[b]	0-10 rating scale (mean score)	Self-report
Perceived influence on government	0-10 rating scale	Self-report
Problems with noise at home	Binary (yes/no)	Self-report
Problems with dust, smell or contamination at home	Binary (yes/no)	Self-report
Area for play and recreation within 200 metres of home	Binary (yes/no)	Self-report
Area for hiking within 500 metres of home	Binary (yes/no)	Self-report
Problems with crime, violence or vandalism in residential area	Binary (yes/no)	Self-report
Worried about violence or threats when walking outside and alone[c]	Binary (Very or somewhat worried/Not worried)	Self-report
Experienced discrimination in the last 12 months (for any reason)[d]	Binary (yes/no)	Self-report
Living in a rural or urban area	—	Registry-data

Notes. [a]Number of people in household was a truncated variable ranging from one to five or more; number of rooms was truncated and ranged from one to 10 or more. [b]This was the mean score of two items assessing trust that the public sector would provide help needed if becoming ill or injured (item 1) and if becoming unable to work (item 2). [c]The responses for this item were recoded to a binary format as reported. The original response options were "Very worried", "Somewhat worried" and "Not worried". [d]This item was an aggregate of multiple binary items (with response options "Yes" and "No") assessing recent experiences of discrimination because of: age, gender, health problems or illness or injury, disability, ethnic background, skin colour, religion, political attitudes, sexual identity, other reason or uncertain reason. Binary environmental characteristics were coded so 0 represented the absence and 1 the presence of the characteristic. Living in a rural area was coded 0 and urban area coded 1.

Statistical analyses

Data Preparation and Network Estimation.

Nonparanormal transformations were conducted for the numeric variables to deal with skewness using the *huge* package (Jiang et al., 2021). To assess potential overlap between nodes ensuing the theoretical selection of variables, we investigated item redundancy with a data-driven approach using the *goldbricker* function in *networktools* (Jones, 2022). No

redundant variables were identified with the minimum zero-order correlation specified to be 0.5 and the threshold proportion of significantly different correlations 0.25. As a sensitivity analysis, we examined topological overlap with the minimum-zero order correlation set to 0.25. No variable pairs were identified as redundant in the sensitivity analysis.

We estimated undirected weighted networks using mixed graphical models (MGMs) with the *mgm* package (Haslbeck & Waldorp, 2020). This estimation approach models joint distributions for the nodes and is appropriate for network analysis with mixed variable types. In a MGM, associations between numeric variables can be interpreted as partial correlations; associations between categorical variables and other variables can be interpreted as averaged regression coefficients (Burger et al., 2022; Haslbeck & Waldorp, 2020). Binary environmental variables were coded so 0 represented 'no' and 1 'yes'. Thus, a positive association between a binary variable and mental health node indicated that the presence of the given characteristic was associated with higher wellbeing or depressive or anxiety symptoms (the full variable coding is reported in the Supplementary Materials). We used the Extended Bayesian Information Criterion (EBIC) for model selection with the gamma hyperparameter set to the recommended default value of .25 (Haslbeck & Waldorp, 2020).

We first estimated three separate networks for wellbeing and anxiety and depressive symptoms. After examining overall connections between these mental health domains and environmental factors, we included the specific items assessing wellbeing aspects and symptoms as individual nodes in the networks to examine granular associations with environmental characteristics. The same environmental factors were included in all networks. As our main aim was to examine broad and fine-grained associations between the different common mental health constructs in the population and environmental characteristics, we estimated networks separately for each mental health construct. This further ensured that

fewer than 30 nodes were included in each estimated network model, which has been recommended to ensure that networks remain interpretable (Blanken et al., 2022).

Analysing the Network Structure.

We examined the overall topology of the networks, such as sparsity in the network, using the *qgraph* package employing the Fruchterman-Reingold algorithm for plotting the network (Epskamp et al., 2012). We also estimated the predictability of each node, which yields an estimate of the extent to which an individual node is predicted by other nodes in the network (Haslbeck & Waldorp, 2018). We estimated the proportion of explained variance for continuous variables and accuracy and normalised accuracy for binary variables. We estimated the out-of-sample predictability using the network models estimated in the main sample and the QoL 2020 data.

Network estimation further allows for the identification of central nodes, which facilitates the understanding of the importance of variables in the network (Borsboom et al., 2021; Epskamp et al., 2018). Strength centrality was calculated by summing all absolute values of edge weights for each node. This quantifies the magnitude of a specific node's direct connections to all other nodes, to yield the overall importance of each node in the network. Strength centrality was visualised using radar plots, as previously recommended in the literature (Ebrahimi et al., 2021).

Evaluating Accuracy and Stability of the Estimated Network Parameters (Network Stability Analysis).

To estimate the accuracy of edge weights, non-parametric bootstrapping was used to obtain the 95% Confidence Intervals (CIs) for the edge weights. We examined the stability of centrality indices (i.e., node strength) using case-dropping bootstrapping, yielding the correlation stability coefficient (CS-coefficient). The CS-coefficient quantifies the stability of the obtained centrality index, indicating the maximum number of cases that can be dropped to

maintain, with 95% certainty, a correlation of .70 or higher with the original centrality indices. It is advisable to have a CS-coefficient of at least .50 (Epskamp et al., 2018). These analyses were based on 1000 bootstrapped samples and were conducted using the *bootnet* package (Epskamp, 2021).

Replication of the results in a large-scale independent sample.

Following the network estimation and main analysis in the QoL 2021 data, we conducted an independent, demographically congruent, and approximately equal-sized replication in a sample of the target population using the QoL 2020 data (N = 15,436 for the networks with overall mental health nodes; N = 15,432 for the networks with separate symptom nodes). Following previous procedures in the literature (Ebrahimi et al., 2021), we examined correlations across the main and replication sample for edge weight and strength centrality estimates to assess the replicability of the estimated networks.

Covariates, Missing Data, and Sensitivity Analyses.

We included several key covariates (gender, age, and sexual orientation) to statistically adjust for these variables in the estimated networks. The covariates gender and sexual orientation were recoded to be dichotomous variables (female/male and heterosexual/other, respectively). As the main research questions focused on examining associations between environmental characteristics and population mental health constructs, the relationships between these variables were visualized after adjusting for the covariates.

Participants with missing data were excluded from analyses, resulting in 1869 exclusions for the overall networks and 1874 for the item-level networks. The discrepancy in sample sizes resulted from a small number who had responded to more than 50% of symptom items and received a symptom score but had missing data for at least one item. Participants were required to have responded to all items to be included in item-level network analyses.

We conducted sensitivity analyses to examine the influence of socioeconomic status (SES) on observed associations, by comparing originally estimated overall mental health networks with (otherwise identical) networks which included four additional SES covariates: household income (registry-based); household debt (registry-based); current employment (operationalised by having worked last week or not; self-reported); and education level (having higher education or not; registry-based). Mean edge weight deviations between networks were negligible and correlations between edge weights estimated in each network were high ($rs > .99$), suggesting that controlling for these SES variables did not result in substantial changes in the estimated relationships. We report these results in the Supplementary Materials (Table S6).

Results

The sample sizes for all networks with overall mental health nodes was 15,618. The sample sizes for all networks with separate symptom nodes was 15,613. We report the results for the networks estimated in the QoL 2021 (main) sample in this section, following reporting guidelines for network analysis (Burger et al., 2022). The R code necessary to reproduce the results of the study is available in a public repository on the Open Science Framework and accessible here: https://osf.io/pn7je/?view_only=fa23a4cabe814566bb7a34a657144ce8

Descriptive statistics

The mean SWLS (sum) score in the full sample was 25.21 (*SD* = 6.59), depression score 1.68 (*SD* = .66), anxiety score 1.48 (*SD* = .61), and the mean age was 48.92 (*SD* = 17.06). Additional descriptive statistics are reported in the Supplementary Materials.

Networks with overall wellbeing, depression, and anxiety nodes

In the network with an overall wellbeing node, the mean absolute edge weight across all nodes (including covariates) was .089. Particularly strong associations were observed between experiencing social relations as supportive and rewarding and higher wellbeing, and

between having experienced recent discrimination and lower wellbeing. Higher wellbeing was also positively associated with housing satisfaction and perceived influence on government.

Highest strength centrality was observed for multiple environmental characteristics, including problems with noise at home, problems with crime, violence, or vandalism in the residential area, problems with contamination at home, worrying about violence or threats when walking outside, and feeling safe when out walking (see Figure 2). The environmental factors with highest strength centrality were strongly associated with each other. For instance, problems with noise and dust, smell or contamination at home were positively associated; worrying about violence or threats when walking alone and feeling safe when out walking in the local environment were negatively associated; and feeling safe when out walking and problems with crime, violence or vandalism in the residential area were negatively associated.

In the network with an overall depression node, the mean absolute edge weight across all nodes (including covariates) was .091. Strong associations were observed between higher levels of depressive symptoms and having experienced recent discrimination and worrying about violence or threats when walking in the residential area, and lower levels of depressive symptoms and perceiving social relations as supportive and rewarding. Having problems with noise at home was associated with more depressive symptoms and higher housing satisfaction with less depressive symptoms. The same environmental nodes had highest strength centrality as in the overall wellbeing network and displayed strong associations with each other.

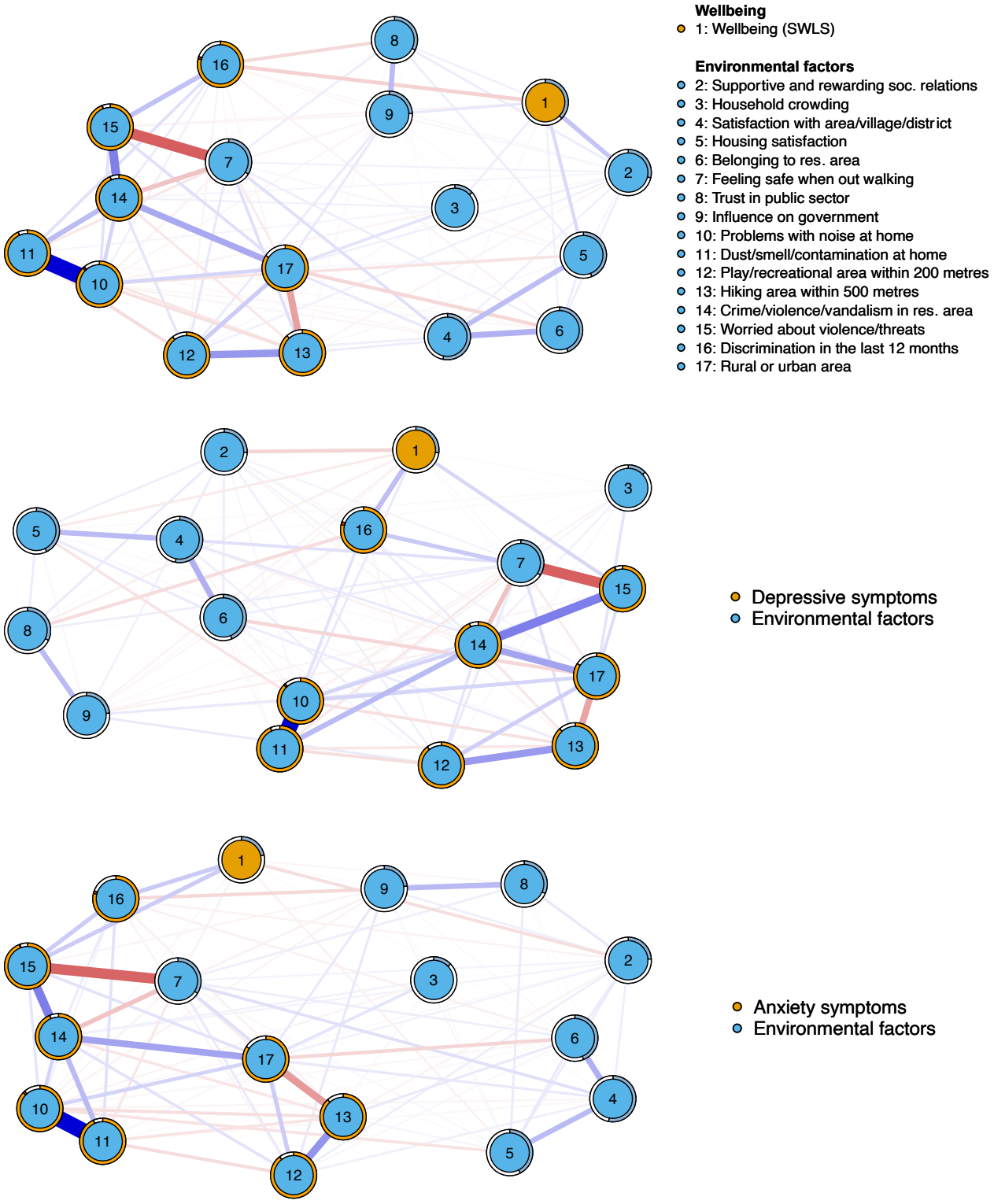
In the network with an overall anxiety node, the mean absolute edge weight across all nodes (including covariates) was .092. Higher levels of anxiety symptoms were associated with worrying about violence or threats when walking in the residential area and having experienced recent discrimination, whereas perceiving social relations as supportive and rewarding was associated with lower anxiety levels. Again, highest strength centrality was

observed for similar environmental factors to the wellbeing and depression networks, which were strongly associated with each other.

The predictability (i.e., proportion of variance explained by other nodes in the network) for the overall mental health nodes was estimated to 37.3% for wellbeing, 27.1% for depressive symptoms, and 21.8% for anxiety symptoms.

Figure 1.

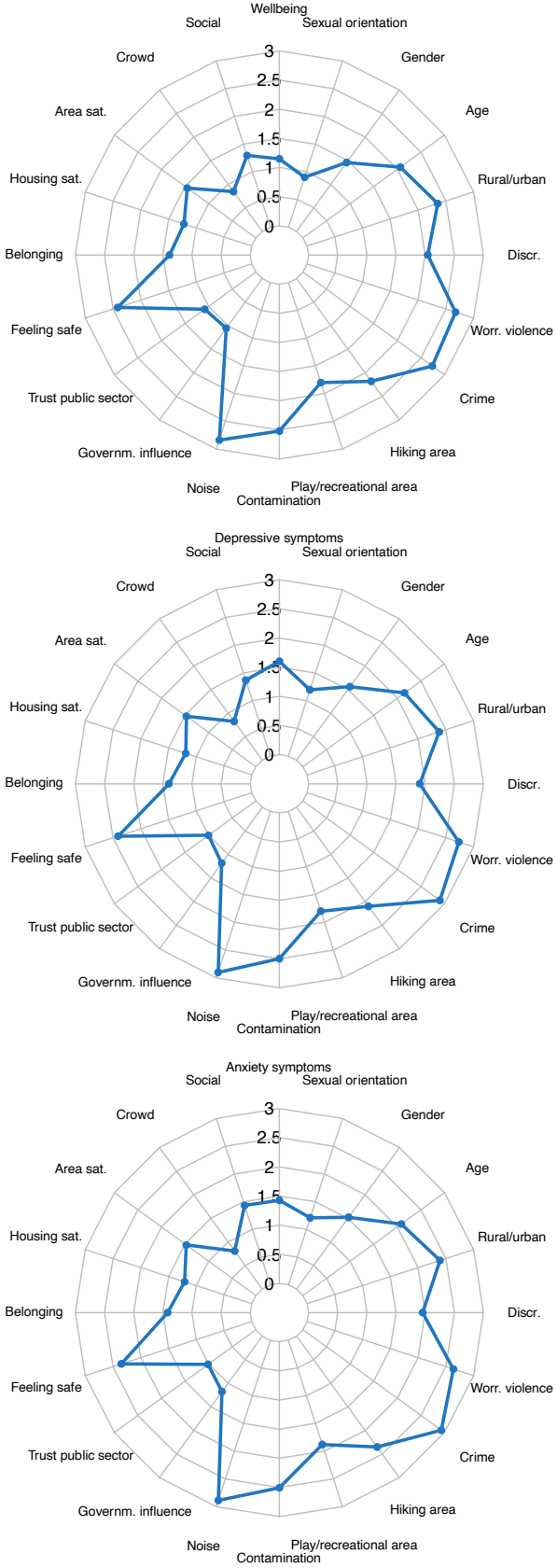
Networks With Environmental Characteristics and Overall Mental Health Nodes.



Notes. Blue edges indicate positive associations and red edges indicate negative associations. For the numeric variables, the blue part of the rings indicates the proportion of variance explained by all other nodes in the network. For the binary variables, the orange part represents the predictability of the intercept model. The red part indicates the additional predictability by including all other nodes in the network. The sum of both (i.e., the red and orange parts) represents the predictability of the full model.

Figure 2.

Strength Centrality Values in the QoL 2021 Sample for Networks with Overall Mental Health Nodes.



Networks with item-specific wellbeing, depression and anxiety nodes

In the network with domain-specific wellbeing nodes, the mean absolute edge weight across all nodes (including covariates) was .072. The strongest associations for the wellbeing nodes were between the item-specific nodes themselves. Among the largest connections between environmental and wellbeing variables, a positive association was observed between life satisfaction and perceiving social relations as supportive and rewarding. More positive appraisal of life conditions was also positively associated with housing satisfaction, trust in the public sector, and perceived influence on government, and negatively associated with having experienced discrimination in the last year. Having gotten the most important things in life was positively associated with household crowding. Highest strength centrality was observed for similar environmental factors as reported for the overall networks. Strength centrality estimates were broadly similar for all item-specific networks (these estimates are reported in the Supplementary Materials).

In the network with symptom-specific depression nodes, the mean absolute edge weight across all nodes (including covariates) was .074. The strongest associations for the depressive symptom nodes were between the symptom-specific nodes themselves. Tying depressive symptomatology to environmental factors, experiencing sleeping problems was positively associated with having experienced discrimination in the last year and having problems with noise at home. Having recently experienced discrimination also had substantial positive associations with feeling hopeless about the future and worrying too much about things. Perceiving social relations as supportive and rewarding had substantial negative associations with both feeling blue and hopeless about the future.

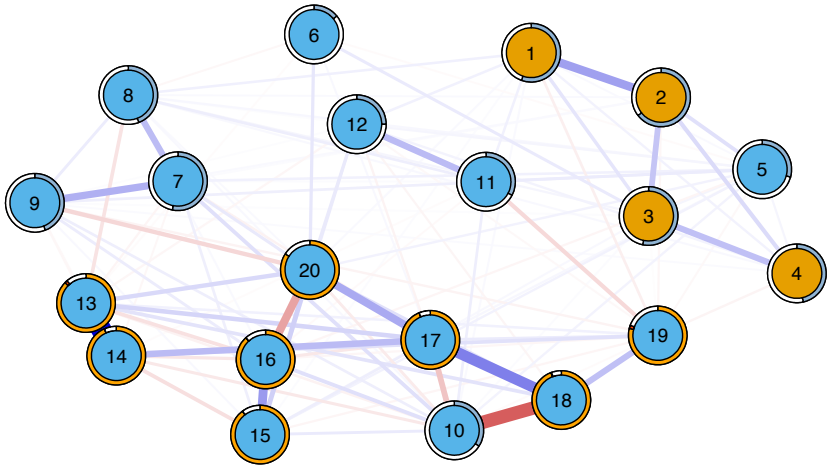
In the network with symptom-specific anxiety nodes, the mean absolute edge weight across all nodes (including covariates) was .073. The strongest associations for the anxiety symptom nodes were between the symptom-specific nodes. The environmental factors and

anxious symptomatology were related through experiencing sudden fear for no reason and being afraid or anxious, which were both positively associated with worrying about violence or threats when walking outside. Moreover, experiencing nervousness or shakiness had a substantial positive association with having experienced discrimination in the last year and negative association with perceiving social relations as supportive and rewarding.

The predictability for the item-level nodes ranged from 46.5% to 64.4% for wellbeing (mean predictability across wellbeing items was 54.9%), from 22.8 to 51.5% for depressive symptoms (mean predictability across depressive items was 43.5%), and from 46.3% to 54.7% for anxiety symptoms (mean predictability across anxiety items was 50.4%).

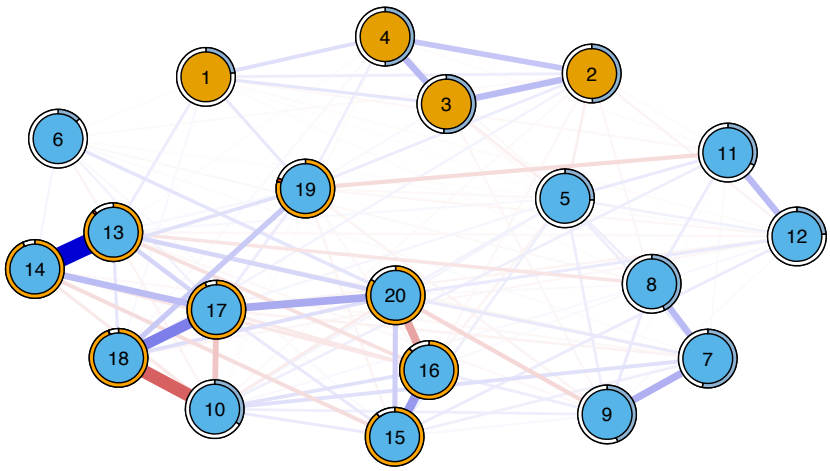
Figure 3.

Networks With Environmental Characteristics and Item-Specific Mental Health Nodes.



Wellbeing
- 1: Life conditions very good
- 2: Satisfaction with life
- 3: Gotten most important things in life
- 4: Change much about life

Environmental factors
- 5: Supportive and rewarding soc. relations
- 6: Household crowding
- 7: Satisfaction with area/village/district
- 8: Housing satisfaction
- 9: Belonging to res. area
- 10: Feeling safe when out walking
- 11: Trust in public sector
- 12: Influence on government
- 13: Problems with noise at home
- 14: Dust/smell/contamination at home
- 15: Play/recreational area within 200 metres
- 16: Hiking area within 500 metres
- 17: Crime/violence/vandalism in res. area
- 18: Worried about violence/threats
- 19: Discrimination in the last 12 months
- 20: Rural or urban area



Depressive symptoms
- 1: Sleeping problems
- 2: Hopelessness
- 3: Feeling blue
- 4: Worried

Environmental factors
- 5: Supportive and rewarding soc. relations
- 6: Household crowding
- 7: Satisfaction with area/village/district
- 8: Housing satisfaction
- 9: Belonging to res. area
- 10: Feeling safe when out walking
- 11: Trust in public sector
- 12: Influence on government
- 13: Problems with noise at home
- 14: Dust/smell/contamination at home
- 15: Play/recreational area within 200 metres
- 16: Hiking area within 500 metres
- 17: Crime/violence/vandalism in res. area
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- 19: Discrimination in the last 12 months
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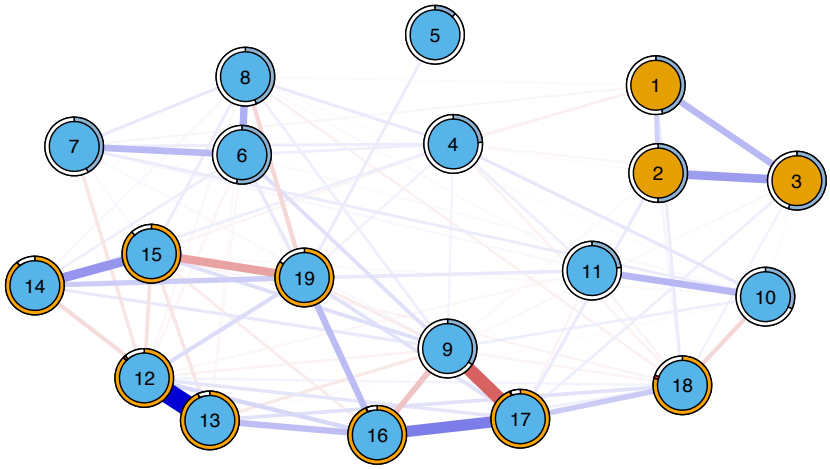

Anxiety symptoms
- 1: Nervousness
- 2: Sudden fear
- 3: Afraid or anxious

Environmental factors
- 4: Supportive and rewarding soc. relations
- 5: Household crowding
- 6: Satisfaction with area/village/district
- 7: Housing satisfaction
- 8: Belonging to res. area
- 9: Feeling safe when out walking
- 10: Trust in public sector
- 11: Influence on government
- 12: Problems with noise at home
- 13: Dust/smell/contamination at home
- 14: Play/recreational area within 200 metres
- 15: Hiking area within 500 metres
- 16: Crime/violence/vandalism in res. area
- 17: Worried about violence/threats
- 18: Discrimination in the last 12 months
- 19: Rural or urban area

Accuracy and stability analysis

Bootstrapped edge weight confidence intervals were narrow for all networks, reflecting high accuracy of the parameter estimates (Epskamp et al., 2018). Overall, the results also suggested that the stability of the obtained centrality estimates was high, with the CS-coefficients estimated to be .75. Results of the accuracy and stability analyses are reported in the Supplementary Materials.

Replicating networks in an independent large-scale sample

The results from all three networks were consistent and robustly replicated across the main sample and the replication sample. The correlation between edge weights comparing the main and replication samples were $r = .974$ for the overall wellbeing network, $r = .973$ for the overall depressive symptoms network, $r = .973$ for the overall anxiety symptoms network, $r = .975$ for the item-specific wellbeing network, $r = .973$ for the separate depressive symptoms network, and $r = .974$ for the separate anxiety symptoms network. Strength centrality estimates were similarly robust across the main and replication samples, with correlations ranging from $r = .944$ to $.974$.

Discussion

We identified associations between multiple environmental characteristics and population mental health across two independent samples of 31,000 adults using network analysis. Our findings yield insights into numerous relationships between environmental factors and population mental health, outlined below.

Perceiving social relations as supportive and rewarding was robustly associated with higher wellbeing and lower levels of depressive and anxiety symptoms. Multiple characteristics of social relationships have been associated with wellbeing in previous studies (Diener et al., 2018), and social support has been associated with several wellbeing aspects in adults (Siedlecki et al., 2014). Experiencing unmet needs for social support has been

associated with both depressive symptoms and major depressive disorder (Barger et al., 2014). Experiencing social isolation has also been associated with depression in community samples (Hawthorne, 2008). Thus, our results align with previous studies in identifying the importance of perceiving the social environment as supportive for population mental health. Theories concerning basic psychological needs, such as self-determination theory (Ryan & Deci, 2017), also highlight the importance of social belonging and connectedness.

Conversely, having experienced discrimination in the last year was associated with higher levels of mental illness symptoms and lower wellbeing. Perceived discrimination has been associated with adverse mental health outcomes in previous studies (Pascoe & Smart Richman, 2009; Schmitt et al., 2014). Furthermore, we found that having experienced discrimination was negatively associated with trust in the public sector and positively associated with worrying about experiencing violence or threats when out walking. This highlights important patterns of connection between environmental factors and population mental health and how such factors are jointly related to each other and to mental health.

We applied network analysis to identify both overall associations with aggregate scores representing mental health constructs and more granular associations on a symptom-level. Moving across levels of aggregation of constructs such as aspects of mental health using network analysis can yield useful insights into the complex relationships of specific factors and mental health (Borsboom et al., 2021; Deserno et al., 2018). Delineating such specific associations can be useful for deeper understanding of how environmental characteristics influence population mental health.

We identified fine-grained associations between environmental characteristics and specific mental health aspects. For instance, perceiving life conditions as good was negatively associated with having experienced recent discrimination and positively associated with housing satisfaction, trust in the public sector, and perceived influence on government. How

satisfied people are with democratic governance has been found to predict both happiness and life satisfaction in previous studies (Orviska et al., 2014). We extend previous findings identifying associations between wellbeing and characteristics of the broader society by highlighting connections between specific wellbeing aspects and environmental factors.

Other specific associations were observed between sleeping problems and having experienced discrimination and having problems with noise at home. These findings are in agreement with findings from several previous studies. A recent study found higher risk of insomnia symptoms associated with perceived racial discrimination (Bethea et al., 2020). Noise in the neighbourhood has been associated with insomnia in multiple studies (Evandt et al., 2017; Hanibuchi et al., 2021). One previous Norwegian study found that sleeping problems were associated with traffic noise (Evandt et al., 2017). Beyond the identification of novel associations between environmental factors, wellbeing, and mental health symptoms, the present study corroborates the robustness of these associations through identification of these links when controlling for the simultaneous presence of a wide range of environmental factors and mental health variables in the same analysis.

Network analysis can also shed light on direct and indirect associations between environmental factors and mental health. For instance, satisfaction with and experienced sense of belonging to residential area were primarily linked to housing satisfaction, which was itself directly connected to mental health in all networks. Perceiving problems with crime in the residential area was associated with worrying about violence or threats when walking outside and alone, but only the latter was directly connected to mental health symptoms. These direct and indirect patterns of association are indicative of how environmental characteristics are linked to population mental health in multifactorial and complex ways.

We also found that environmental factors were strongly associated with each other and had a similar profile of influence across all networks. The most strongly connected nodes in

all networks represented environmental characteristics, supporting the notion that environmental factors are related to population mental health through different and specific pathways (van der Wal et al., 2021). Evidence of the relevance of included variables and their direct and indirect relationships with mental health is provided by the proportions of explained variance (predictability estimates) for the overall mental health nodes, ranging from 22% for anxiety symptoms to 37% for wellbeing.

Strengths and limitations

The present study has multiple strengths. First, we estimated networks in two large and population-based samples of randomly drawn individuals from Norway. Second, we included items assessing both multiple aspects of population mental health and numerous environmental characteristics. Third, we assessed associations between environmental factors and population mental health at multiple levels of aggregation. Fourth, we conducted an out-of-sample replication of the estimated networks in an independent sample, which provided evidence of high replicability and the robustness of the estimated networks.

Our study also has some limitations. First, the cross-sectional nature of both samples and self-report data limit opportunities for assessing if and which environmental characteristics have a causal influence on population mental health. We cannot exclude the possible influence of recall bias, i.e., if current mental states influenced responses to items. For instance, it may be that individuals with depressive symptoms report lower housing satisfaction in part because of the symptoms themselves (e.g., sadness), rather than low housing satisfaction causing depressive symptoms. Directionality in observed associations is also rendered unclear by the nature of the data (e.g., worrying about violence may increase anxiety symptoms but individuals with anxiety symptoms may also worry more about violence in the residential area). Our results should be interpreted taking these limitations into account. Second, limitations of centrality estimates have been described elsewhere

(Bringmann et al., 2019). Importantly, it has been found high structural connectedness, e.g., suggested by centrality measures, may not in and of itself be indicative of the importance of nodes in a network (Quax et al., 2013; van Elteren et al., 2022). Thus, strength centrality estimates in the present study should not be interpreted as highlighting the most important environmental factors for mental health, e.g., for intervention or prevention efforts. Third, although a representative random sample was drawn from the Norwegian population, the final sample, due to attrition, include some overrepresentation of respondents with higher education, in the age group 45-66 years, and with a Norwegian country background. Fourth, our measurements of both wellbeing, anxiety and depressive symptoms consisted of brief questionnaires, which yield rough measurements of substantially heterogeneous constructs. Depressive symptoms were not clinically assessed, which is typically considered "gold standard" (Stuart et al., 2014). Finally, we statistically adjusted for living in a rural or urban area but did not examine differences in networks across counties in Norway. As only Norwegian data was used, the generalizability of our findings to other countries is also unclear.

Implications

Although further research is needed to establish the causal nature of the observed associations, our findings support the notion that environmental characteristics are related to population mental health in distinct ways and are also intricately linked with each other (van der Wal et al., 2021). Multiple environmental factors, such as experiencing problems with noise or contamination at home, crime, violence or vandalism in the residential area, and worrying about violence or threats when walking outside and alone, had notable connectedness in the networks. Several environmental characteristics can potentially serve as useful targets for public health efforts seeking to improve population mental health. For instance, 'greening' interventions have been associated with improved community mental

health (South et al., 2018) and 'place-based' interventions for violence prevention emphasise addressing neighbourhood factors to reduce violence (Gobaud et al., 2022). Our identification of substantial associations between population mental health and environmental factors such as problems with noise and contamination are notable in light of the limited research on mental health and climate events (e.g., pollution, greenspace; Cuijpers et al., 2023).

Future research is needed to better understand relationships between environmental characteristics and population mental health. Longitudinal data would be beneficial to assess temporal associations and the dynamic between fluctuating environmental characteristics and mental health over time. Intensive longitudinal data collection, such as ecological momentary assessment, could be particularly useful for this purpose (van der Wal et al., 2021). Studies with designs that are not cross-sectional are needed to understand which environmental factors causally influence mental health. Future studies could account for interrelationships between mental health constructs by including these in the same networks, in light of the high interrelatedness of psychopathology symptoms (Campbell & Osborn, 2021; McElroy et al., 2019). Furthermore, future research could examine links between environmental factors and clinically assessed disorders. Finally, future studies could specifically investigate aspects of SES which influence associations between environmental factors and mental health.

Conclusion

We applied network analysis to examine relationships between environmental characteristics and multiple aspects of population mental health in two independent large-scale population-based random samples of adults. We found evidence of numerous associations between environmental factors and mental health. Perceiving social relations as supportive and rewarding and having experienced discrimination in the last year were robustly associated with wellbeing, anxiety symptoms, and depressive symptoms. There were distinct patterns of connection between the environmental characteristics and mental health.

Replicability of the results was strong and indicative of robustness of the results across samples. Although further research is needed to examine temporal and causal influences on environmental characteristics on mental health, several factors represent potentially useful candidate targets for public health efforts seeking to improve population mental health.

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III

IV

Disentangling direct and indirect genetic effects from partners and offspring on maternal depression using trio-GCTA

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Word count (excl. Abstract, Tables, Figures, References): 4023.
Keywords: depressive symptoms, maternal depression, trio-GCTA, indirect genetic effects

Abstract

Maternal depressive symptoms are highly prevalent and can negatively impact affected individuals and family members. Understanding aetiological influences on maternal depression, such as genetic liability, is key to inform treatment and prevention efforts. In the present study, we quantified direct and indirect genetic effects (i.e., when genetic variants in other individuals influence risk of maternal depression through the environment) from partners and offspring on maternal depressive symptoms at multiple timepoints using genome-wide complex trait analysis with parent-offspring trios. We used data from the Norwegian Mother, Father and Child cohort study, including up to 21,000 genotyped parent-offspring trios. Models with indirect genetic effects had best fit at three of five timepoints (3, 5, and 8 years after birth). The variance in maternal depressive symptoms explained by direct genetic effects ranged from 5-14%, while indirect genetic effects explained 0-14% of variance across timepoints. Heritable traits in family members contribute to maternal depressive symptoms through the environment at several timepoints after birth.

Introduction

Many women experience the onset of depressive symptoms during the postpartum period (Gavin et al., 2005; O'Hara & McCabe, 2013; O'Hara & Swain, 1996). Depression and depressive symptoms experienced by mothers, which we refer to here using the term 'maternal depression', may persist for several years (S. M. Horwitz et al., 2007, 2009), and can have negative impacts for affected individuals, children, partners, and the broader family system. It has been associated with adverse child outcomes such as concurrent child psychopathology symptoms (Gjerde et al., 2017, 2021), disturbances in mother-offspring interactions (Field, 2010), and detrimental effects on parental and family functioning (Letourneau et al., 2012; Lovejoy et al., 2000). Negative effects of maternal depression both for affected women and the broader family highlight the need for effective treatment and preventive interventions. Understanding aetiological influences, including both individual and family-level factors, is key to inform such efforts.

Several individual characteristics increase risk of maternal depression, such as a history of psychiatric illness (Guintivano et al., 2018) and adverse life events (S. M. Horwitz et al., 2007). Depression in women is moderately influenced by genetic factors, with heritability estimates (i.e., the proportion of phenotypic variance explained by genetic variance) at around 40% (Polderman et al., 2015; Sullivan et al., 2000). Although few studies have examined the heritability of maternal depression specifically, similar and slightly lower heritability estimates for postpartum depression and depressive symptoms have been reported (Samuelsen et al., 2023; Treloar et al., 1999; Viktorin et al., 2016). Recent genome-wide association studies (GWAS), which seek to identify single nucleotide polymorphisms (SNPs) associated with outcomes, have identified a number of independent genetic variants associated with adult depression and depressive symptoms (Howard et al., 2019; Levey et al.,

2021; Wray et al., 2018). Thus, recent GWAS studies have yielded novel insights into the genetic architecture of adult depression.

Maternal depression may also be influenced by characteristics of the partner and the quality of the partner relationship. For instance, it has been found that higher relationship satisfaction and partner involvement reduces risk of depressive symptoms (S. M. Horwitz et al., 2007; Pilkington et al., 2015). Other relationship-related factors associated with risk of depressive symptoms include higher levels of conflict, worse communication, lack of emotional support, and lack of instrumental support (Pilkington et al., 2015). As a result, several preventative interventions for maternal depression aim to improve skills in communication and conflict resolution (Werner et al., 2015).

Characteristics of children in the family may also increase risk of maternal depression. Difficult infant temperament has been associated with increased risk of depressive symptoms in multiple studies (Austin et al., 2005; Beck, 2001; Britton, 2011; McGrath et al., 2008). Studies have also found that psychopathology symptoms and sleep problems in children can influence parental depressive symptoms using both genetically informative (Ahmadzadeh et al., 2019; McAdams et al., 2015) and longitudinal (Landolt et al., 2014; Ystrom et al., 2017) designs.

Given that maternal depression is related to partially heritable partner and child characteristics, it is possible that genetic effects on maternal depressive symptoms may act indirectly, as well as directly. While direct genetic effects occur when genetic variants in one individual influence depression risk for that same individual, indirect genetic effects are dependent on the genes of other individuals (Kong et al., 2018; McAdam et al., 2014; Young et al., 2019). For instance, genetic variants can exert a direct effect on depression risk in an individual (e.g., a child) as they are inherited, and those variants could also indirectly influence another person's risk (e.g., their mother) through their behaviour (i.e., indirect

genetic effects from child to mother via the environment). Studies have identified both evocative genotype-environment correlation, whereby genetically influenced phenotypes in children evoke reactions in other people (Fearon et al., 2015; Ge et al., 1996; McAdams et al., 2015), and genetic effects mediated by parental behaviour (Cheesman et al., 2020; Eilertsen et al., 2022; Kong et al., 2018). Most GWAS studies seek to identify direct genetic effects yet may inadvertently tag indirect genetic effects. Some studies use family designs, such as estimating within-sibship effects by incorporating data from siblings, to account for parent to offspring indirect genetic effects (Howe et al., 2022).

To examine direct and indirect genetic effects on maternal depression, trio genome-wide complex trait analysis (trio-GCTA; Eilertsen et al., 2021) can be used. Trio-GCTA is an extension of GCTA, a statistical method in which heritability is estimated based on SNPs across a chromosome or the full genome (Yang et al., 2010, 2011, 2017). Trio-GCTA utilises genotyped data from mothers, partners, and children, and can disentangle direct and indirect genetic effects of mothers, partners, and children on maternal depression, as illustrated in Figure 1.

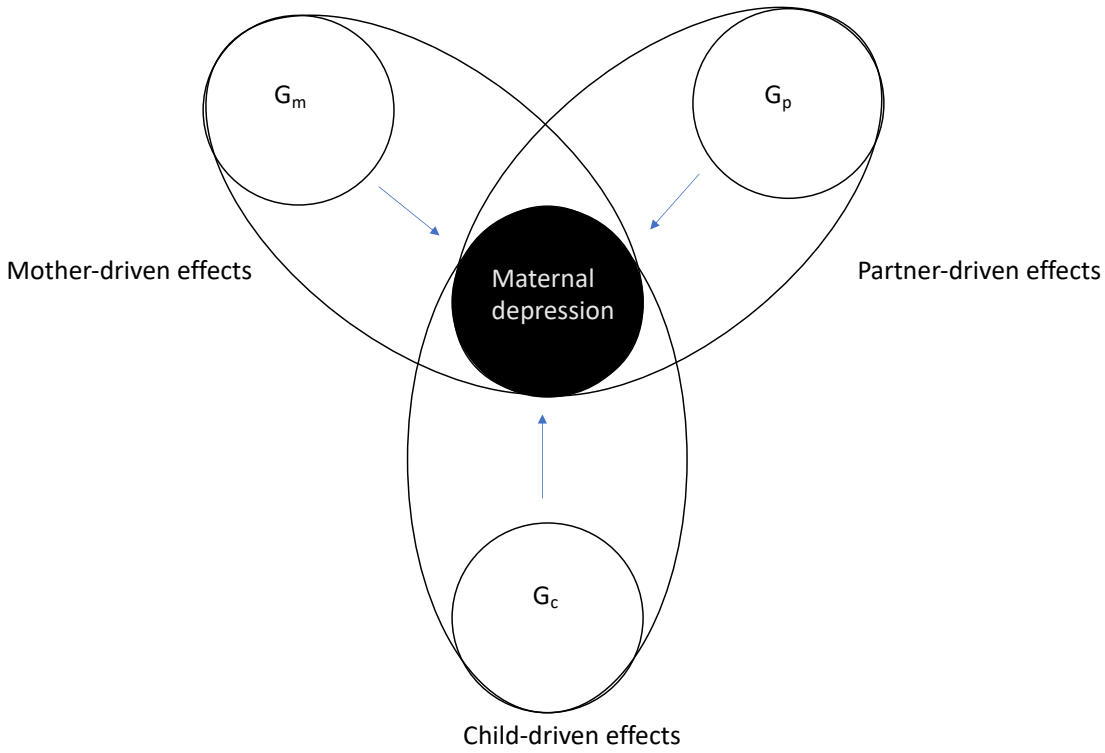
The trio-GCTA approach has several strengths, above and beyond allowing for the quantification of direct and indirect genetic effects on a phenotype. Firstly, it eliminates risk of reverse confounding, i.e., if the observed association between a risk factor and an outcome at least in part reflects the influence of the outcome on the risk factor. This is a limitation of most observational studies of risk factors for depression. In the trio-GCTA framework, partner- and child-driven effects are based on genomic data and cannot be explained by reverse confounding, as depressive symptoms in the mother cannot change DNA sequences in other individuals (i.e., partner and child). Secondly, trait-based models which examine indirect genetic effects (e.g., polygenic scores calculated using untransmitted alleles) are limited by the scope of included phenotypic measures, wherever less than all relevant partner

and offspring traits are assessed. Variance-component approaches such as trio-GCTA allow for estimating the *total* contribution of indirect genetic effects without the need to measure partner and offspring traits.

In the present study, we aim to estimate genetic effects on maternal depressive symptoms using trio-GCTA with parent-offspring data from the Norwegian Mother, Father and Child Cohort Study (MoBa; Magnus et al., 2016). The sample comprises mothers with five measurement points from six months after birth until eight years after birth. We aim to quantify the influence of direct and indirect genetic effects on maternal depressive symptoms at each timepoint, separating mother-driven, partner-driven, and child-driven effects.

Figure 1.

Conceptual Model of Mother-, Partner- and Child-Driven Effects on Maternal Depression.



Notes. Figure 1 illustrates hypothetical effects on risk of maternal depression risk which can be estimated using trio-GCTA. *Mother-driven effects* represent direct genetic effects on maternal depressive symptoms. *Partner-driven* and *child-driven* effects reflect indirect genetic effects from partners and offspring, respectively.

Methods

Participants

Participants were recruited from MoBa (Magnus et al., 2016), a population-based study conducted by the Norwegian Institute of Public Health, for which all pregnant Norwegian women were eligible to participate. Invitations to participate were sent to 277,702 women and the participation rate was 41%. In total, the cohort consists of 114,500 children, 95,200 mothers and 75,200 fathers. We used data from version 12 of the quality-assured MoBa data files. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The present study was approved by the Regional

Committees for Medical and Health Research Ethics (project number: 2013/863). The genotype pipeline for the MoBa study is described in Corfield et al. (2022), which involved retaining only participants with European ancestry genotype data. Details specific to the current analysis are further described in the Supplementary Materials.

Selection of parent-offspring trios

The quality control of genotype data retained 25,332 complete mother-father-offspring trios. We used parent-offspring trios with data on maternal depressive symptoms collected at five timepoints after birth: 6 months, 1.5 years, 3 years, 5 years, and 8 years. Sample sizes decrease across the measurement time points mainly due to attrition, which has been described elsewhere (Magnus et al., 2016). We estimated a genetic relatedness matrix, which represents an empirical estimate of the genetic relatedness among all individuals in the sample (Yang et al., 2011). We used a threshold of 0.10 for the largest genetic correlation allowed between any two individuals (ignoring pairs of parents and offspring), to limit confounding due to closely related individuals being included in analyses (Yang et al., 2017). This threshold has been applied in previous trio-GCTA studies with the aim of excluding closely related individuals while maintaining a large number of parent-offspring trios (Eilertsen et al., 2022; Eilertsen, Jami, et al., 2021). We computed the GRM and selection of individuals using the 'bottom up' algorithm with functions from the OpenMendel project (Zhou et al., 2020). Final sample sizes at each timepoint after birth (number of trios) were 21,146 at 6 months, 17,789 at 1.5 years, 13,888 at 3 years, 10,360 at 5 years, and 10,582 at 8 years.

Measures

Maternal depressive symptoms in the last 14 days were assessed using an eight-item short form version of the Symptom Checklist (SCL) (Hesbacher et al., 1980; Tambs & Røysamb, 2014). This measure has been previously validated (Fink, Ørnbøl, Hansen, et al.,

2004; Fink, Ørnbøl, Huyse, et al., 2004). Individual sum scores of the four depressive symptoms in the SCL were created for each timepoint. A single measure was used for mothers with more than two questionnaires at a single timepoint (i.e., if mothers had more than one child). We randomly chose one child for inclusion in the analyses (and used the associated symptom measure) for mothers of multiple children in MoBa. We applied a logarithmic transformation to the symptom sum scores to reduce skewness. The scores were then standardised using the mean score and standard deviation at the first timepoint (i.e., 6 months after birth), so that means and standard deviations at later timepoints can be interpreted relative to this.

Trio-GCTA

The statistical approach in GCTA has been termed genomic relatedness matrix (GRM) restricted maximum likelihood (GREML) and uses a mixed linear model to estimate heritability with genomic data (Yang et al., 2010, 2011, 2017). It is assumed that SNPs contribute to phenotypic variation and that these effects correlate between individuals with similar genotypes. The GREML approach quantifies the SNP-based heritability (Yang et al., 2017), i.e., the effects tagged by genotyped and imputed SNPs used in the analysis. This heritability estimate is therefore dependent on the set of SNPs which have been collected. GCTA has typically been used in samples of unrelated individuals, but was extended by Eaves et al. (2014) to also include data from mothers and offspring, allowing for the estimation of maternal indirect genetic effects. Eilertsen et al. (2021) extended this method to estimate indirect genetic effects from any individual in parent-offspring trios (trio-GCTA).

In the present study, the focal individuals were mothers and parameters are interpreted with reference to maternal depressive symptoms. The variance components which are estimated are:

$$Var(y_k) = \sigma_m^2 + \sigma_p^2 + \sigma_o^2 + \sigma_{om} + \sigma_{op} + \sigma_e^2$$

σ_m^2 represents the variance explained by direct genetic effects; σ_p^2 and σ_o^2 the variance explained by partner and offspring indirect genetic effects, respectively; σ_{om} the covariance between maternal direct genetic effects and offspring indirect genetic effects; σ_{op} the covariance between indirect partner and offspring genetic effects; and σ_e^2 the residual variance of the phenotype. The residual variance estimate may include genetic effects not captured by SNPs included in the analysis, unique environmental effects, and shared environmental effects not captured by SNPs. The covariance between direct maternal genetic effects and partner indirect genetic effects (σ_{mp}) is estimated, but not expected to contribute to variance in maternal depressive symptoms, as parents are not related. Several assumptions are made in trio-GCTA. Genetic and residual effects are assumed to follow a multivariate normal distribution. The different genetic effects can be dependent but individual SNP effects are assumed to be independent. Furthermore, it is assumed that random mating occurs in the population. It has recently been shown that assortative mating for depressive symptoms in MoBa does not seem to be substantial (Ayorech et al., 2023).

We tested 5 models per timepoint, as reported in Table 1. The first model estimated all variance components (i.e., the full model). The subsequent models estimated fewer parameters, dropping either the covariance parameters for the direct and indirect genetic effects (Model 2), or one indirect genetic effect and covariance (Models 3 and 4). The final model estimated only direct genetic effects and the error component. Each model included the fixed effects of child sex, genotype batches, imputation batches, and principal components of mothers and fathers. Model fit was assessed using Akaike's Information Criteria (AIC) (Akaike, 1987). The model considered to have best fit at each timepoint was the model with the lowest AIC value. We also conducted likelihood ratio tests where we compared the goodness of fit of the full model with the nested models (i.e., Models 2-5). However, there are challenges regarding the interpretation of likelihood ratio tests with

family data (Dominicus et al., 2006; Wu & Neale, 2013). We are not aware of work examining interpretation of likelihood ratio tests in the context of GREML methods which involve direct and indirect genetic effects. We therefore relied on AIC for selecting models with best fit at each timepoint. The models were estimated using the Julia programming language (Bezanson et al., 2017), via the package VCModels.jl (Eilertsen, 2021).

Table 1.

Models and Variance Components Estimated in Each Model.

Model	Parameters estimated
1. Full model (all effects)	$\sigma_m^2;\ \sigma_p^2;\ \sigma_o^2;\ \sigma_{om};\ \sigma_{op};\ \sigma_{mp};\ \sigma_e^2$
2. No covariances between direct and indirect effects	$\sigma_m^2;\ \sigma_p^2;\ \sigma_o^2;\ \sigma_e^2$
3. Direct and offspring indirect effect	$\sigma_m^2;\ \sigma_o^2;\sigma_{om};\sigma_e^2$
4. Direct and partner indirect effect	$\sigma_m^2;\ \sigma_p^2;\ \sigma_{mp};\sigma_e^2$
5. Direct genetic effects only	$\sigma_m^2;\ \sigma_e^2$

Notes. σ_m^2 represents the variance explained by direct genetic effects; σ_p^2 and σ_o^2 the variance explained by partner and offspring indirect genetic effects, respectively; σ_{om} the covariance between maternal direct genetic effects and offspring indirect genetic effects; σ_{op} the covariance between indirect partner and offspring genetic effects; and σ_e^2 the residual variance of the phenotype.

Results

We evaluated intrafamilial influences on maternal depressive symptoms at 6 months, 1.5 years, 3 years, 5 years, and 8 years after birth using SNP data from parent-offspring trios. Models including indirect genetic effects had best fit at 3, 5, and 8 years after birth, however differences in AIC values between the competing models were small. Therefore, we focus on characterising the total contribution of indirect genetic effects, instead of comparing the absolute contributions of partner and offspring effects. Likelihood ratio tests (at 5% level) generally suggested a similar pattern of model fit as AIC values. We report the parameter estimates and model fit statistics for each model per timepoint in Table 2. Figure 2 shows the variance decomposition at the different timepoints with parameter estimates from the best-fitting models.

In general, the proportion of explained variance in depressive symptoms by genetic effects (comprising both direct and indirect effects) was larger at later timepoints after birth (i.e., from 3 years after birth and onwards). The variance in maternal depressive symptoms explained by direct genetic effects in the models with the lowest AIC values was 8% at 6 months after birth, 7% at 1.5 years, 14% at 3 years, 5% at 5 years, and 13% at 8 years after birth (see Table 2). The proportion of variance explained by both offspring and partner indirect genetic effects was 14% at 3 years after birth. Offspring indirect genetic effects explained 10.5% of variance at 5 years after birth, which was more than the variance explained by direct genetic effects. Partner indirect genetic effects explained 6% of variance at 8 years after birth.

At 3 years after birth, the covariance between direct maternal and indirect offspring genetic effects was negative and the correlation was -0.63, indicative of a negative gene-environment correlation. Covariances between direct and indirect genetic effects at 5 and 8 years were close to zero.

Table 2.

Parameter Estimates and Fit Statistics for Each Model Specification.

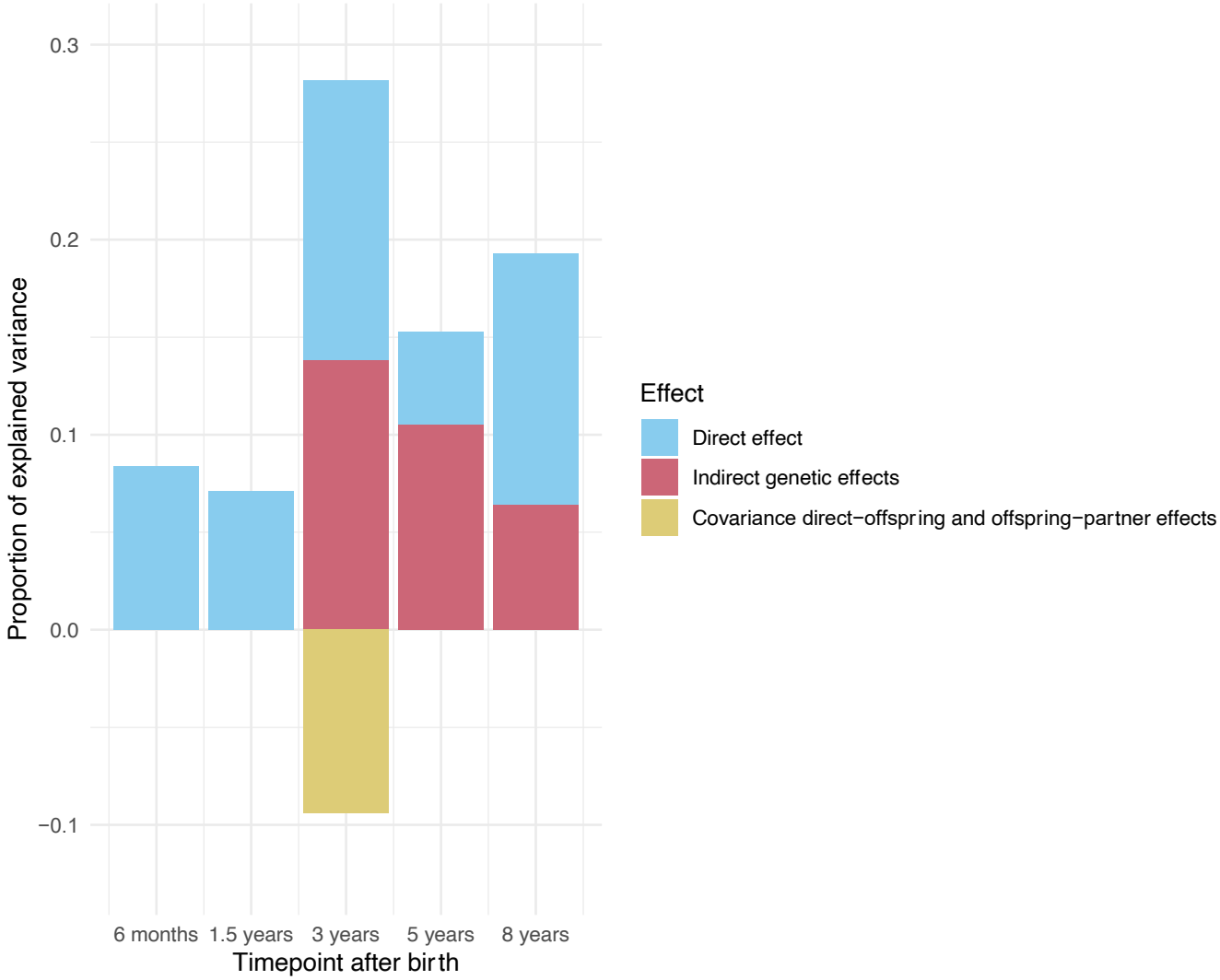
	Parameters										
Timepoint after birth	σ_m^2 **(SE)**	σ_p^2 **(SE)**	σ_o^2 **(SE)**	σ_{mp} **(SE)**	σ_{om} **(SE)**	σ_{op} **(SE)**	σ_e^2 **(SE)**	**-2ll**	**AIC**	**df**	**p-value**
6 months											
Full model	.099 (.023)	.003 (.007)	.016 (.023)	.010 (.015)	-.019 (.020)	.003 (.009)	.898 (.022)	58924.21	59042.21	59	—
No covariances	.081 (.016)	.005 (.016)	.009 (.017)	—	—	—	.906 (.023)	58925.87	59037.87	56	.64
Direct and offspring indirect effect	.092 (.020)	—	.021 (.021)	—	-.014 (.017)	—	.901 (.022)	58925.27	59037.27	56	.79
Direct and partner indirect effect	.083 (.015)	.006 (.015)	—	.007 (.011)	—	—	.910 (.021)	58925.72	59037.72	56	.68
Direct genetic	**.084 (.015)**	**—**	**—**	**—**	**—**	**—**	**.916 (.015)**	**58926.34**	**59034.34**	**54**	**.83**
1.5 years											
Full model	.070 (.027)	.003 (.025)	.041 (.036)	.008 (.020)	-.011 (.026)	-.002 (.024)	.898 (.031)	52273.83	52391.83	59	—
No covariances	.061 (.018)	.003 (.019)	.035 (.020)	—	—	—	.901 (.027)	52274.12	52386.12	56	.96
Direct and offspring indirect effect	.065 (.024)	—	.041 (.026)	—	-.005 (.020)	—	.900 (.026)	52274.08	52386.08	56	.97
Direct and partner indirect effect	.069 (.018)	.011 (.018)	—	.012 (.012)	—	—	.920 (.025)	52276.15	52388.15	56	.51
Direct genetic	**.071 (.017)**	**—**	**—**	**—**	**—**	**—**	**.929 (.017)**	**52277.62**	**52385.62**	**54**	**.58**
3 years											
Full model	**.144 (.035)**	**.039 (.034)**	**.099 (.048)**	**.062 (.026)**	**-.075 (.034)**	**-.019 (.034)**	**.813 (.040)**	**41000.48**	**41118.48**	59	—
No covariances	.082 (.024)	.032 (.023)	.055 (.026)	—	—	—	.832 (.034)	41009.14	41121.14	56	.03
Direct and offspring indirect effect	.107 (.031)	—	.095 (.033)	—	-.035 (.025)	—	.833 (.033)	41009.10	41121.10	56	.03
Direct and partner indirect effect	.094 (.023)	.043 (.022)	—	.040 (.016)	—	—	.863 (.032)	41007.53	41119.53	56	.07
Direct genetic	.097 (.023)	—	—	—	—	—	.903 (.023)	41018.51	41126.51	54	.00
5 years											
Full model	.053 (.046)	.002 (.012)	.123 (.061)	.007 (.029)	-.009 (.043)	-.013 (.035)	.845 (.043)	28660.66	28778.66	59	—

No covariances	**.048 (.032)**	**.000 (.000)**	**.105 (.034)**	**—**	**—**	**—**	**.846 (.039)**	**28660.84**	**28772.84**	**56**	**.98**
Direct and offspring indirect effect	**.048 (.041)**	**—**	**.105 (.042)**	**—**	**-.000 (.033)**	**—**	**.846 (.043)**	**28660.84**	**28772.84**	**56**	**.98**
Direct and partner indirect effect	.079 (.031)	.010 (.014)	—	.028 (.020)	—	—	.912 (.032)	28669.44	28781.44	56	.03
Direct genetic	.078 (.031)	—	—	—	—	—	.922 (.031)	28671.08	28779.08	54	.06
8 years											
Full model	.154 (.043)	.045 (.032)	.011 (.017)	-.014 (.026)	-.027 (.030)	.019 (.016)	.797 (.043)	31532.67	31650.67	59	—
No covariances	.128 (.031)	.063 (.031)	.000 (.000)	—	—	—	.809 (.043)	31534.82	31646.82	56	.54
Direct and offspring indirect effect	.164 (.042)	—	.025 (.041)	—	-.038 (.033)	—	.850 (.043)	31537.67	31649.67	56	.17
Direct and partner indirect effect	**.129 (.031)**	**.064 (.031)**	**—**	**-.014 (.022)**	**—**	**—**	**.807 (.043)**	**31534.40**	**31646.40**	**56**	**.63**
Direct genetic	.130 (.031)	—	—	—	—	—	.870 (.031)	31539.09	31647.09	54	.27

Notes. Bold values indicate the model specification with the lowest AIC estimate for each timepoint. σ_m^2 represents the variance explained by direct genetic effects; σ_p^2 and σ_o^2 the variance explained by Partner and offspring indirect genetic effects, respectively; σ_{om} the covariance between maternal direct genetic effects and offspring indirect genetic effects; σ_{op} the covariance between indirect partner and offspring genetic effects; and σ_e^2 the residual variance of the phenotype. P-values below .05 (the threshold value for statistical significance) indicate that a given model exhibited a worse fit than the full model in a likelihood ratio test. P-values above .05 indicate that a given model did not demonstrate a significantly worse fit compared with the full model.

Figure 2.

Estimates of Direct and Indirect Genetic Effects at Separate Timepoints.



Notes. Figure 2 shows the parameter estimates from best-fitting models at each timepoint. The variance components are standardised and sum to 1, so that the remaining variance not accounted for is explained by residual error (not shown in Figure 2). Sample sizes were 21,146 at 6 months, 17,789 at 1.5 years, 13,888 at 3 years, 10,360 at 5 years, and 10,582 at 8 years. The covariance between direct effects and partner indirect genetic effects is not expected to contribute to variance in maternal depressive symptoms and is therefore not shown in Figure 2.

Discussion

In a large-scale sample including up to 21,000 Norwegian parent-offspring trios, we found evidence of direct genetic effects at all timepoints and indirect genetic effects from partners and/or offspring on maternal depressive symptoms at 3, 5, and 8 years after birth.

Although our data did not allow us to select specific models which distinguished effects from family members, models with indirect genetic effects had better fit for these timepoints. Thus, these findings highlight the importance of considering intrafamilial effects, such as partner and offspring indirect genetic effects, on maternal depressive symptoms across the early childbearing years.

The variance explained by direct genetic effects for maternal depressive symptoms from the best-fitting models ranged from 5% (5 years after birth) to 14% (3 years after birth). Thus, we found varying heritability estimates across timepoints after birth. It would be useful for future studies to investigate heterogeneity in estimates of direct genetic effects on maternal depressive symptoms to determine if varying estimates across timepoints are linked to timepoint-specific genetic and environmental influences or methodological aspects (e.g., related to trio-GCTA or statistical power). Given the limited ability to distinguish alternative models, we cannot separate sampling variability from true heterogeneity across time in the current analysis.

In this study, estimates of direct genetic effects on maternal depressive symptoms are not confounded by indirect effects, which may wrongly be attributed to direct genetic effects if not accounted for (Young et al., 2018). Comparisons of heritability estimates to previous findings are further complicated by heterogeneous operationalisations of depression across studies (Cai et al., 2020), sample differences, and analysis differences. Our estimates of direct genetic effects are lower than what has been reported in several previous studies, in which the SNP-based heritability of major depressive disorder has been estimated to 21% (Lee et al., 2013), 32% (Lubke et al., 2012), and depressive symptoms to 21% (Laurin et al., 2015). Furthermore, our sample differs from these studies in that we quantified direct genetic effects in mothers only, which could contribute to observed differences. In addition, we assessed depressive symptoms in the last 14 days, which would be expected to have lower heritability

than life-time diagnoses of depression. Previous twin studies have found that the heritability of lifetime risk of major depressive episode diagnoses is substantially higher than of depression risk in a given year (e.g., Bjørndal et al., 2022). Our estimates are closer to heritability estimates reported in previous GWAS studies of diverse depression phenotypes (Howard et al., 2019; Levey et al., 2021; Wray et al., 2018).

Interestingly, the variance explained by direct genetic effects on maternal depressive symptoms at 8 years after birth (14%) was similar to the variance explained by indirect genetic effects (of mothers and fathers) on child depressive symptoms at the same time-point, as estimated in a previous study in this cohort (Cheesman et al., 2020). Cheesman et al. (2020) also found that the indirect effects were partly mediated by a measure of maternal anxiety and depressive symptoms.

Our findings are broadly in line with the conceptualisation of maternal depression as a family-wide mental illness (Ayorech et al., 2022; Letourneau et al., 2012), the risk of which is influenced both by individual factors (e.g., direct genetic effects), and family-level characteristics, as has been shown previously (Madigan et al., 2017). The results of the present study suggest that genetic effects from both partners and offspring, mediated through the environment, contribute to maternal depressive symptoms at multiple timepoints after birth. Thus, both partner and offspring indirect genetic effects may represent family-level factors influencing depressive symptoms. Nevertheless, given the limited ability to statistically distinguish alternative models, uncertainty regarding the magnitude of specific parameter estimates should be considered relatively large. A particular strength of the trio-GCTA approach is that all indirect genetic effects from partners and offspring at each timepoint are quantified without having to rely on a wide range of measures of such environmental effects. Furthermore, there is no risk of reverse confounding, which may otherwise limit observational studies of risk factors for maternal depression based on self-

report data. Thus, indirect genetic effects index environmental influences while eliminating common methodological artifacts such as recall bias.

The prevalence of depressive symptoms in MoBa mothers was higher at 18 months and three years after birth compared with six months postpartum, while continuing to increase for mothers with multiple births (Ystrøm et al., 2014). Our results indicated that indirect genetic effects contributed to maternal depressive symptoms at child age 3 and beyond, influencing risk of maternal depressive symptoms at these timepoints. It is possible that indirect genetic effects on depressive symptoms arise when family resources are more limited, for instance as many parents will have returned to the workforce after parental leave when children are aged three and older. Offspring indirect genetic effects could also possibly reflect phenotypes subject to early development, for instance related to sleep, language, and temperament. Previous studies have suggested that genetic factors which influence adult depressive and anxiety symptoms are mostly the same across timepoints in adulthood (Nes et al., 2007; Nivard et al., 2015). Future studies could examine the stability of direct and indirect genetic effects on maternal depressive symptoms and if these influences involve the same or different SNPs across time in longitudinal analyses.

At 3 years after birth, results indicated that there was a negative gene-environment correlation for direct genetic and offspring indirect genetic effects. This suggests that the same genes in mothers and offspring work in opposite directions with regards to maternal depressive symptoms at this timepoint. We note that a negative correlation between direct and indirect genetic effects was also found in a recent study of ADHD using trio-GCTA with the child at 8 years as the focal individual (Eilertsen et al., 2022). Eilertsen et al. (2022) highlight that negative correlations between genetic effects of children and parents could help sustain genetic variation in populations across time, which has been argued elsewhere on the basis of animal studies (Räsänen & Kruuk, 2007). In the present study, the observed negative

gene-environment correlation could for instance arise if children of parents with high genetic risk of depressive symptoms are inclined to exhibit behaviours which tend to reduce risk of depressive symptoms. This also implies that indirect genetic effects could suppress the heritability estimate for maternal depression in studies not including family members.

Trio-GCTA is a variance decomposition approach which benefits from not requiring the comprehensive measuring of all relevant partner and offspring traits to quantify indirect genetic effects. Therefore, we examined indirect genetic effects while remaining agnostic to specific phenotypes involved in these influences. Future studies of indirect genetic effects using trait-based models may investigate possible traits and mechanisms.

Our study has several limitations which should be kept in mind when interpreting the results. First, differences between the competing models with regards to model fit statistics (AIC and likelihood values) were generally small. Therefore, the statistical support in favour of any specific model deemed best-fitting should not be interpreted as strong. Second, we cannot exclude the possible influence of selection bias or bias due to attrition in MoBa (Biele et al., 2019; Nilsen et al., 2009). Furthermore, our sample was restricted to women with children and their partners and a Norwegian context, and the study was based on European ancestry genotype data, limiting the generalizability of our findings beyond this group. Third, estimates of indirect genetic effects can be biased by assortative mating and population stratification, as demonstrated in polygenic score studies of educational outcomes (Cheesman et al., 2023; Demange et al., 2022). Partner correlations for depression phenotypes are typically moderate in magnitude (T. B. Horwitz et al., 2023; Peyrot et al., 2016), which has been found in MoBa also (Eilertsen, Hannigan, et al., 2021; Torvik et al., 2022). When assortative mating occurs for a trait, it is generally expected to increase the heritability of the trait. However, two recent studies, both using polygenic scores, did not find evidence of widespread assortative mating for depression in MoBa (Ayorech et al., 2023; Sunde et al.,

2023). We note that these studies may have yielded estimates which are biased downwards because of low predictive power of the depression polygenic score itself. Torvik et al. (2022) identified a small genetic correlation among MoBa partners for depression using a structural equation modeling approach. How assortative mating would bias estimates and inferences derived from trio-GCTA is currently uncertain (Eilertsen, Jami, et al., 2021). Future studies should examine the extent that estimates of indirect genetic effects on depression from trio-GCTA may also capture bias from factors such as assortative mating and population stratification (Eilertsen et al., 2022; Eilertsen, Jami, et al., 2021).

Conclusion

In the present study, we quantified direct and indirect genetic effects on maternal depressive symptoms in MoBa at 5 measurement time points after birth. We found support for offspring and partner indirect genetic effects on depressive symptoms in mothers at 3, 5, and 8 years after birth. Our results point to the importance of considering intrafamilial effects, such as indirect genetic effects from other family members, for understanding risk for maternal depressive symptoms. These indirect genetic effects operate through the environment and contribute to risk of maternal depressive symptoms at several timepoints after birth. Thus, our results illustrate the utility of genomic designs and the trio-GCTA method in investigating environmental influences on maternal depressive symptoms using genetic data. Most importantly, our study shows that heritable traits in close family members have a directional environmental effect on depressive symptoms in women during childbearing years.

Acknowledgements

The authors declare no competing interests.

Data availability statement

MoBa data can be accessed by application to the Regional Committee for Medical and Health 494 Research Ethics in Norway and MoBa (https://www.fhi.no/en/ch/studies/moba/for-forskere-artikler/research-and-data-access/). The consent given by the participants does not open for storage of data on an individual level in repositories or journals.

Code availability statement

The code used in this study is available upon request from the first author.

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