

# The nature of the relation between mental well-being and ill-being

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Research on mental health has traditionally separated the study of ill-being, including clinically defined mental and behavioural disorders and subthreshold problems, from the study of well-being, which encompasses factors such as life satisfaction and positive affect. Although previous reviews of studies primarily using self-report scales indicate that ill-being and well-being are distinct yet interconnected constructs, a deeper examination of their relationship is lacking. In this Perspective, we synthesize genetic, biological, developmental, psychosocial, societal, cultural and clinical research on ill-being and well-being. Our review reveals substantial genetic overlap and similar biological underpinnings for ill-being and well-being. By contrast, environmental factors and societal changes often exert divergent influences. We propose a differentiated multidisciplinary framework in which the shared and unique determinants, predictors, mechanisms and consequences of mental ill-being and well-being vary across levels of analysis, offering a more nuanced understanding of the interconnections.

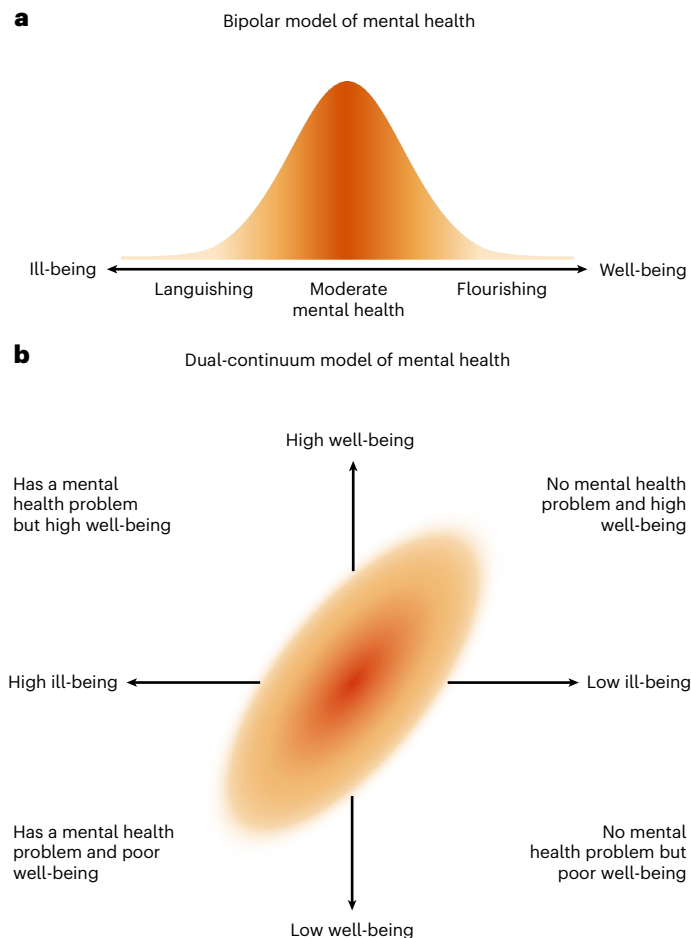
Mental health disorders and problems, which we here refer to as mental ill-being, substantially contribute to the global burden of disease. The lifetime prevalence rate for any mental disorder has been estimated to be in the 50–80% range, with anxiety, mood, impulse-control and substance use disorders being the most common<sup>1,2</sup>. Mental disorders cause inherent suffering and increase the risk of adverse outcomes such as work absence, suicide and mortality<sup>3,4</sup>. In addition to diagnostically defined disorders, mental health problems vary along dimensions of severity and dysfunctionality, with subthreshold symptoms adding to the overall disease burden worldwide<sup>5</sup>. Common mental disorders tend to co-occur and share causes and consequences, leading researchers to develop hierarchical models including a general dimensional *p*-factor<sup>6,7</sup>. However, whether conceived in categorical or dimensional terms, ill-being is typically conceptualized as a deviation from normative or adaptive patterns of mental functioning.

Partly independent of research on mental ill-being, the scientific study of mental well-being has grown rapidly in recent decades<sup>8</sup>. Mental well-being can be defined as people's overall positive evaluations of their lives and emotional experiences and includes happiness, life satisfaction, positive affect, meaning, and engagement<sup>9,10</sup>. Well-being is considered a universal human value and defined as a United Nations Sustainable Development Goal<sup>11</sup>, and well-being indicators

are increasingly used alongside economic indicators to guide social progress<sup>12</sup>. Beyond the intrinsic value of human well-being, evidence indicates that well-being promotes daily functioning, health, social relations, workforce engagement and longevity<sup>8,13</sup>. As with ill-being, the umbrella term 'well-being' encapsulates components that differ (for example, eudaimonic versus hedonic<sup>14</sup>) but nonetheless can be summarized by a latent factor *h* (ref. 15).

But what is the nature of the relationship between mental ill-being and well-being? This question has been the subject of debate for decades. Some scholars advocate for the bipolar model, proposing a uni-dimensional continuum with ill-being and well-being positioned at opposite ends of a single continuum<sup>16</sup> (Fig. 1a). In this model, ill-being and well-being are closely intertwined, with each being defined as the direct opposite of the other. Conversely, the dual-continuum model represents a two-dimensional view, asserting that ill-being and well-being are represented on distinct continua<sup>17</sup> (Fig. 1b). This model emphasizes the need to conceptualize ill-being and well-being on distinct dimensions, although a negative correlation between the two is typically observed. A literature review has recommended that correlations stronger than  $-0.40$  provide empirical support for a bipolar model, whereas weaker correlations align more with a dual-continuum model<sup>18,19</sup>. However, beyond empirical correlations, theoretical criteria

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**Fig. 1 | Models of mental health.** **a**, Bipolar model, proposing a single continuum for mental health, with ill-being and well-being positioned at opposite ends of a normal distribution. **b**, Dual-continuum model, proposing a two-dimensional framework, with ill-being and well-being as separated yet interrelated dimensions.

have also been proposed for determining bipolarity<sup>20,21</sup>. These criteria include confirming the independent existence of each construct, identifying evidence that disconfirms a bipolar structure and assessing functional independence between mental ill-being and well-being. Researchers also emphasize the importance of testing these models at the subdomain levels rather than relying solely on global measures of mental ill-being and well-being<sup>20</sup>.

A recent scoping review of 83 empirical articles found overall support for a dual-continuum model, specifically a two-factor oblique model<sup>22</sup>. However, the studies included in the review primarily used self-report scales and were cross-sectional, leaving many questions about the interconnectedness of mental ill-being and well-being at other levels of analysis unanswered. To what extent do they have distinct or shared genetic and environmental underpinnings, and brain structural and functional correlates? Are they temporally related across the lifespan? And importantly, are they shaped and modified by the same or different social structures, policies and interventions? Previous attempts to elucidate the nature of the relationship between ill-being and well-being lack interdisciplinary integration, and there is a need for comprehensive multilayered joint models. Here we consolidate research across different levels of analysis, advocating for a multilevel framework that bridges existing gaps. Such a comprehensive approach substantially enhances our current understanding of the complex relationship between mental ill-being and well-being.

**Table 1 | Multilevel influences on ill-being and well-being**

Level of influences	Examples
Genetic	Numerous genome-wide genetic variants contribute small proportions to the phenotypic variance in mental health and interact with environmental factors. Interindividual genetic variability thereby contributes to differences in ill-being and well-being.
Biological	Hormonal changes during puberty affect mood and mental health. Variations in the timing of puberty and gender-specific hormonal changes may thus contribute to individual and gender differences in ill-being and well-being.
Psychosocial	Stable and emotionally fulfilling social relationships are essential for mental health. Supportive social environments across the life-course—in both childhood and adulthood—can therefore influence levels of ill-being and well-being.
Cultural and societal	Social welfare systems that address inequality and support vulnerable populations can promote mental health at the societal level. Cross-national differences in ill-being and well-being may partly reflect variation in welfare policy and implementation.

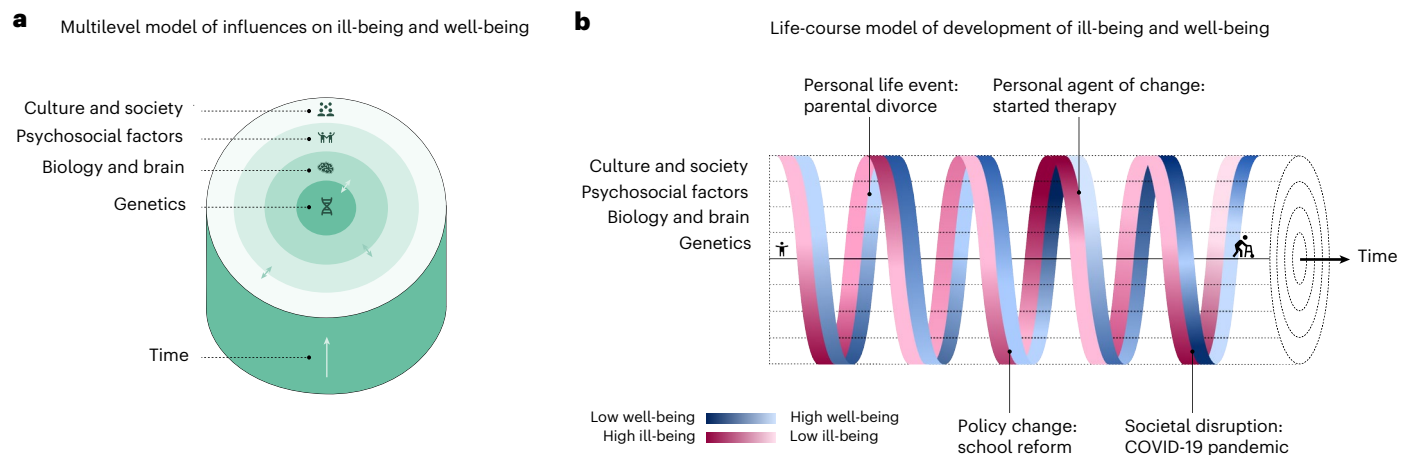
The table summarizes a multilevel model of influences on ill-being and well-being, with examples spanning genetic, biological, psychosocial and cultural–societal domains.

We conducted a literature search on mental ill-being (including ‘depression’, ‘depressive’, ‘anxiety’ and ‘internalizing’) and well-being (including ‘life satisfaction’, ‘well-being’, ‘wellbeing’, ‘happiness’, ‘happy’ and ‘quality of life’) using the Web of Science (Supplementary Information). The search identified 1,568,321 international publications on the selected ill-being indicators and 1,655,307 publications on the selected well-being indicators. However, only 7.2% of the papers included both categories jointly. Research into mental ill-being and research into well-being thus seem to largely operate in isolation, with limited attention to their interconnected nature. A framework that integrates both phenomena holds promise for providing new insights into both groups of conditions and elucidating human mental functioning in general. Beyond theoretical importance, understanding the nature of the relationship between mental ill-being and well-being has substantial implications for prevention, intervention and public health strategies<sup>19</sup>. If mental health is conceptualized merely as the absence of mental health problems, opportunities for early intervention, resilience-building and well-being promotion may be overlooked, ultimately constraining efforts to foster positive mental health at both the individual and societal levels.

The aim of this Perspective is to move beyond the phenotypic level by adopting an interdisciplinary and dynamic life-course viewpoint on the relationship between mental ill-being and well-being. We review key findings on the shared and independent nature of ill-being and well-being across multiple levels of analysis, including genetic, biological, developmental, psychosocial, and cultural and societal levels (Table 1 and Fig. 2a), and propose a differentiated framework in which the nature of their relationship varies across levels. Moreover, across these levels and in a separate section on intervention research, we emphasize the importance of considering individual lifespan development, societal changes and historical events in shaping ill-being and well-being (Fig. 2b). Rather than providing an in-depth analysis of any single level, this Perspective aims to synthesize insights across disciplines, offering a broad and integrative viewpoint on the complex interplay between mental ill-being and well-being.

## Genetic perspectives

Mental ill-being and well-being are influenced by an interplay of genetic and environmental factors, which have been studied using various genetically informative methods. Twin and family studies can estimate



**Fig. 2 | Multilevel life-course model of ill-being and well-being.** **a**, Illustration of multilayered influences shaping mental ill-being and well-being, including genetic, biological, psychosocial, and cultural and societal factors. The bidirectional arrows in the model highlight the dynamic interplay between these levels over time, including how societal factors shape psychosocial environments, influence biological processes and modulate gene expression.

**b**, Illustration of how individual lifespan trajectories of mental ill-being and well-being are shaped by genetic, biological, psychosocial, and cultural and societal factors. The model highlights the effect of these influences over time and how key personal and societal events may influence the trajectories of ill-being and well-being in distinct ways. It also underscores the role of timing, as developmental stages may moderate these effects.

heritability, which indicates the extent to which trait variation can be attributed to genetic variation in a given population. Heritability estimates are approximately 40% for several components of both ill-being and well-being<sup>23–25</sup>, although estimates vary across specific conditions and components<sup>26–28</sup>.

Advances in genetic methods now allow for the use of DNA data from unrelated individuals to estimate heritability from common genetic variants, known as single nucleotide polymorphisms (SNPs). SNP-based heritability, which considers only the additive effects of a subset of genetic variants tagged by current DNA arrays, is generally lower than twin-based heritability, ranging from 1% to 20% for both ill-being and well-being<sup>29,30</sup>. Beyond estimating heritability, genome-wide association studies (GWAS) seek to identify the genetic variants associated with traits of interest. GWAS of ill-being and well-being have identified several genome-wide significantly associated SNPs, each of which account for a very small proportion of phenotypic variance (<1%)<sup>31–33</sup>. However, when these SNPs are combined into polygenic scores, they can be used to further our understanding of the antecedents and correlates of ill-being and well-being across development<sup>34</sup>.

Genetic methods make it possible to estimate the overlap in genetic and environmental influences on ill-being and well-being. Multivariate twin and genomic analyses have shown that genetic factors in ill-being and well-being have high negative correlations, ranging from –0.60 to –1.00 across different measures<sup>32,35,36</sup>. This suggests that most genetic variants associated with risk of ill-being are also linked to lower well-being, supporting a bipolar model at the genetic level. However, a recent study using GWAS-by-subtraction, a method that isolates genetic variation specific to a trait by removing genetic variation associated with other traits, identified genetic factors linked to well-being that are independent of depressive symptoms<sup>37</sup>. This finding suggests that, although substantial genetic overlap exists, well-being may also have distinct genetic influences separate from those contributing to depression.

Genetic methods also inform about the correlation between environmental components of ill-being and well-being. Non-shared environmental correlations are lower than genetic correlations, ranging from –0.05 to –0.30 (refs. 35,38). This suggests that environmental factors tend to be specific to either ill-being or well-being. However, the non-shared environment component in twin studies includes measurement error, which may partly explain these low correlations.

Multiple possible mechanisms can lead to genetic and environmental correlations<sup>39</sup>, including direct effects of ill-being on well-being, but these mechanisms remain to be empirically understood.

Twin studies have found little evidence that environmental factors shared by children growing up in the same family (that is, the shared environment) have a substantial effect on either ill-being or well-being later in life when genetic effects are taken into account<sup>40</sup>. However, societal and cultural factors operating at the national level represent a type of shared environment that often has been overlooked in twin studies, which typically examine within-nation variation<sup>41</sup>. In addition, genetic and family shared environment factors are often correlated. Recent developments in genomic approaches have shown that parents' heritable traits influence ill-being in their children through the environment<sup>42</sup>. Parents' ill-being has been associated with children's ill-being over and above genetic transmission<sup>43</sup>; yet there are also recent indications that such intergenerational social effects could be going from the child to the parent<sup>44,45</sup>. Studies evaluating the familial gene–environment interplay jointly for ill-being and well-being are lacking, however. In summary, genetically informed studies indicate a substantial degree of genetic overlap between well-being and ill-being, while environmental influences may be largely distinct.

## Biological perspectives

The brain is a major locus of integration for the multitude of genetic and environmental factors that shape our lives. Neural mechanisms therefore constitute important pathways connecting these factors to mental ill-being and well-being. A wealth of studies has examined associations between genetic and phenotypic expressions of mental health problems and brain structure and function<sup>46,47</sup>. Large-scale magnetic resonance imaging studies have found that several mental disorders are associated with subtle structural brain differences, including smaller surface area and thickness as well as subcortical volumes<sup>47</sup>. For instance, depression is associated with thinner cortex in the prefrontal and temporal regions, lower hippocampal volumes, and white matter microstructural alterations, although the effects vary across the lifespan and stages of illness, with smaller cortical surface area observed only in adolescent depression<sup>48,49</sup>. Furthermore, meta-analyses have shown overlapping neuroimaging findings for several mental disorders, a sort of neural *p*-factor<sup>50</sup>, suggesting that many mental disorders share neural underpinnings.



Fewer studies have examined the associations between well-being and brain structure and function. A systematic review of 56 studies reported inconsistent findings pertaining to both the brain regions involved and the direction of the associations<sup>51</sup>. The discrepant findings are probably in part a result of underpowered studies with small samples. A recent large-scale study of adults found that higher well-being scores were associated with regionally larger cortical surface area and lower cortical thickness, although the effect sizes were small<sup>52</sup>. Additionally, polygenic scores for well-being were positively associated with cerebellar volumes and supramarginal surface area, but there was no genetic correlation between self-reported well-being and brain structure, suggesting no direct genetic drivers<sup>52</sup>.

The small amount of variance in ill-being and well-being attributable to neuroimaging measures highlights the potential value of network and multimodal approaches. This will allow the examination of widespread neural systems and the combination of multiple imaging metrics to further examine unique mechanisms. Furthermore, while emerging depression in adolescence has been found to coincide with faster age-expected frontal cortical thinning<sup>53</sup>, larger longitudinal studies are needed to map how brain maturation and ageing coincide with the development, fluctuations and course of ill-being and well-being across the lifespan. Moreover, although it has been argued that the precision with which we measure behavioural phenotypes, including ill-being and well-being, should be addressed<sup>54</sup>, the measurement of neuroimaging features could also probably be improved.

Beyond structural and functional characteristics of the brain, a systematic review of well-being and physiological markers indicates potential roles of serotonin, cortisol and inflammation<sup>55</sup>. The directions of these associations were the inverse of what has been found for these markers in depression<sup>56,57</sup>, suggesting shared biological mechanisms underlying ill-being and well-being. Further studies on other physiological markers, such as sex hormones, in relation to ill-being and well-being are needed<sup>58</sup>. Importantly, recent work suggests that combining neuroimaging and other biological metrics could hold great promise in advancing our understanding of how different facets of biological ageing relate to ill-being and well-being<sup>59</sup>. In summary, existing neuroimaging and physiological studies suggest some shared biological mechanisms underpinning mental ill-being and well-being. However, multivariate and longitudinal studies examining both ill-being and well-being in the same samples are needed to probe shared and distinct mechanisms and life-course dynamics.

## Developmental and psychosocial perspectives

Life-course development of mental ill-being and well-being may be expected to show similar patterns if they share a common underlying continuum. In adolescence, evidence for converging trends has been provided by a large-scale longitudinal study, revealing increasing levels of depressive symptoms alongside a decrease in well-being from ages 11 to 14 (ref. 60). Interestingly, this study also found that the well-known sex differences emerging in adolescence for depression were paralleled by emerging sex differences in well-being, disfavouring girls<sup>60</sup>; however, studies in the adult population show few sex differences in well-being<sup>61</sup>. Early studies on adult life satisfaction have indicated a U-shaped trajectory across age in many countries, with the highest well-being scores among young and old adults and lower levels in midlife<sup>62</sup>. However, recent research obtained heterogeneous findings, with age trends varying according to the population, study characteristics and measures used<sup>63</sup>. Although research is limited, studies examining the adult lifespan development of ill-being suggest a U-shaped trajectory in depressive symptoms, with the lowest symptom levels occurring in midlife and higher levels in early and late adulthood<sup>64</sup>. Together, research from developmental psychology indicates that mental ill-being and well-being trends converge in adolescence but show less consistency in adulthood.

A related issue is whether psychosocial factors affect ill-being and reduced well-being in similar ways. Deficits in self-regulation have been proposed as a key vulnerability for ill-being<sup>65,66</sup>, and strong self-regulation capacities are identified as important assets in promoting well-being<sup>67</sup>. Results from meta-analyses underscore the importance of self-regulation by showing substantial similarities in how the personality domain of conscientiousness is related to reduced ill-being ( $r = -0.30$ )<sup>68</sup> and increased well-being ( $r = 0.36$ )<sup>69</sup>. Likewise, neuroticism, often considered a primary risk factor for psychopathology, exhibits not only considerable correlations with ill-being ( $r = 0.39$ )<sup>68</sup> but also comparable inverse correlations with well-being ( $r = -0.46$ )<sup>69</sup>. However, meta-analytic results demonstrate substantial differences in how other broad personality traits relate to ill-being and well-being. In particular, agreeableness shows very small associations with reduced ill-being ( $r = -0.02$ )<sup>68</sup> but considerable associations with increased well-being ( $r = 0.25$ )<sup>69</sup>. Similarly, extraversion shows stronger associations with measures of well-being ( $r = 0.37$ )<sup>69</sup> than with ill-being ( $r = -0.24$ )<sup>68</sup>.

In the social domain, theoretical accounts highlight the fundamental human need for belongingness, proposing that frequent, stable and emotionally fulfilling interactions are crucial determinants for both well-being and ill-being<sup>70</sup>. Consistent with this view, feelings of social isolation, such as loneliness, show similarly sized associations with well-being and ill-being, including depression, anxiety and overall mental health problems, with correlations ranging from  $r = 0.42$  to  $0.50$  (ref. 71). A large-scale network study further substantiates these findings by demonstrating robust associations between perceiving social relations as supportive and rewarding and both higher well-being and lower ill-being levels<sup>72</sup>.

In summary, research shows similar developmental patterns for ill-being and well-being in adolescence, but the data are insufficient to draw conclusions about the convergence or divergence of adult trajectories. Factors such as self-regulation, neuroticism and social embeddedness appear to be of substantial importance for both ill-being and well-being, as evidenced by similarly sized correlations. These findings align with a continuous view of the nature of mental ill-being and well-being. However, when the roles of other broad personality traits are examined, associations differ, pointing towards unique mechanisms that challenge a unified conceptualization of ill-being and well-being along a single continuum.

## Societal and cultural perspectives

A deeper understanding of the relationship between mental ill-being and well-being may also be gained from demography, secular trends and cross-cultural research. The Gallup World Poll, which covers annual assessments of well-being (defined as life evaluation and positive emotions) and ill-being (defined as negative emotions) from adult samples in 157 countries worldwide, indicates that the most satisfied nations tend to report lower levels of negative emotions. Yet, trend analyses from 2006 onwards indicate that negative emotions have increased sizably and globally since 2010–2011, while well-being has remained fairly stable<sup>73</sup>. International studies of adolescents similarly indicate that ill-being in terms of common mental disorders<sup>74</sup>, health service use and medical prescriptions has increased alongside a negative<sup>60</sup> or more stable<sup>75</sup> trend for well-being (that is, life evaluations). Well-being levels stayed strikingly stable during the COVID-19 pandemic<sup>76</sup>, while negative emotions and the prevalence of both depressive and anxiety disorders increased<sup>77</sup>. Emotion trends based on social media usage from 170 countries during COVID-19 also diverge for different indicators of ill-being and well-being<sup>78</sup>. While fear substantially decreased over the course of the pandemic, anger, joy and sadness increased. The collective findings indicate that at the societal level, well-being does not merely reflect the opposite of ill-being. They also demonstrate that global stressors do not necessarily decrease well-being, at least not at the average national level, and that the associations differ by sociodemographics and specific individual-level indicators.

Are the societal predictors of ill-being and well-being overlapping or distinct? Macro-level factors such as gross domestic product, social capital, educational development and perception of corruption predict both ill-being and well-being, but with associations varying in strength<sup>76,79</sup>. At the individual level, family and personal socio-economic status are also key societal predictors, shaping both ill-being and well-being through multiple pathways, including access to resources, exposure to stress and opportunities for social mobility<sup>80</sup>. Our current knowledge on predictors, causes and consequences of ill-being and well-being, however, is mostly based on European and North American samples. As cross-national differences are likely to be important determinants, research on more diverse country samples is highly warranted<sup>8</sup>. Cultures also differ in how well-being is understood<sup>81</sup>. The measurement tools currently available could therefore reflect cultural variability rather than pure differences in ill-being and well-being. For example, a recent international study indicates that life satisfaction questions tend to underestimate the role of interdependent or collectivistic happiness<sup>82</sup>. The relationship between ill-being and well-being therefore depends on which specific measures are considered.

Taken together, international demographic research indicates that mental ill-being and well-being vary at least partly together across nations and in relation to societal factors, while secular trend research, including research on the effect of the COVID-19 pandemic, overall supports a dual-continuum model. Further research in non-Western countries, including the development of culturally sensitive measurement tools, is needed. Moreover, research on the effect of large-scale societal changes in the domains of technology, economy and climate on mental ill-being and well-being is critical, as discussed below.

### Insights from intervention research

Research on interventions aimed at reducing ill-being or improving well-being may further deepen our understanding of their interrelation. In this context, positive psychology interventions (that is, interventions designed to enhance well-being) are relevant, as evaluations of such interventions frequently assess both well-being and ill-being outcomes. Meta-analytical findings support the beneficial effects of these interventions, with a slightly larger effect on ill-being (Hedge's  $g = -0.39$  for depression and  $-0.62$  for anxiety) than on well-being ( $g = 0.39$ )<sup>83</sup>. A recent mega-analysis of meta-analyses examining positive psychology intervention effects across diverse outcomes replicated these modest differences ( $g = -0.42$  for depression,  $-0.41$  for anxiety,  $-0.42$  for stress,  $0.34$  for general well-being,  $0.42$  for strengths and  $0.41$  for quality of life)<sup>84</sup>.

Psychotherapy research can also illuminate the relationship between ill-being and well-being. A meta-analysis on psychotherapy for depression showed positive effects on different outcomes, with larger reductions in depressive symptoms ( $g = 0.60$ ) than increases in indicators of well-being such as quality of life ( $g = 0.33$ )<sup>85</sup>. Similar results were obtained in another meta-analysis on outcomes of cognitive behavioural therapy and antidepressant treatment, indicating greater reductions in depression ( $g = 1.30$ ) than improvements in quality of life ( $g = 0.69$ )<sup>86</sup>.

While much of this research is based in high-income countries, studies in low- and middle-income countries often focus on interventions designed to improve people's overall life circumstances, and how such interventions may influence both ill-being and well-being. For example, a comprehensive meta-analysis of cash transfer programmes revealed modest positive effects on ill-being (Cohen's  $d = 0.07$ ) and slightly more pronounced effects on well-being ( $d = 0.13$ )<sup>87</sup>. Overall, findings indicate that diverse interventions generally decrease ill-being and increase well-being, providing indications for underlying commonalities. Nonetheless, the magnitude of these effects can vary depending on the specific outcome investigated. For example, interventions targeting depression seem to be more effective in reducing ill-being rather than enhancing well-being.

### Discussion

The phenotypic relationship between mental ill-being and well-being has been extensively examined, but there is a lack of studies that adopt an interdisciplinary approach to this issue. Consequently, there is a need for insights into how ill-being and well-being are interconnected across multiple analytic levels, including genetic, biological, psychosocial and societal domains. In this Perspective, we integrate knowledge from various fields to enhance our understanding of the shared and distinct character of ill-being and well-being.

Our review highlights the complex nature of the relationship between mental ill-being and well-being. While some evidence supports a unidimensional continuum, other findings are consistent with a dual-continuum model. Genetically informed studies reveal substantial genetic overlap between ill-being and well-being, suggesting shared genetic influences consistent with a single continuum. However, these studies also emphasize largely distinct environmental influences, supporting a dual-continuum perspective. Neuroimaging and physiological research provide preliminary evidence for shared biological mechanisms underlying both conditions, although the empirical evidence with regard to well-being and direct comparisons remain limited. Findings on psychosocial and personality factors are mixed. Research on self-regulation, neuroticism and social embeddedness suggests these factors to be of equal importance for ill-being and well-being. By contrast, other personality traits such as extraversion and agreeableness exhibit differently sized associations, with stronger links to well-being. At the societal level, cross-national research adds further complexity. While ill-being and well-being tend to vary together across countries, their time trends often do not align. Our review also considers the differential effects of interventions on ill-being and well-being, demonstrating that most interventions typically affect both dimensions, though to different degrees depending on the intervention.

To summarize, our interdisciplinary review presents empirical support for both a single continuum and a dual-continuum model, depending on the level of analysis. We therefore propose a differentiated perspective in which the relationship between mental ill-being and well-being varies across levels of investigation, from genes to societies. To advance the field beyond existing frameworks, we introduce a multilevel interplay model, which conceptualizes this relationship as context-dependent rather than fixed along a single or dual continuum. As illustrated in Fig. 2, and inspired by bioecological models<sup>88</sup>, this framework integrates genetic dispositions, biological mechanisms, psychosocial factors, and cultural and societal influences to explain when and why ill-being and well-being align or diverge.

Given the substantial overlap in genetic influences and biological substrates, we suggest that they mainly function as broad, shared determinants and mechanisms. In line with this notion, we suggest that overlapping genetic factors predispose individuals to both ill-being and well-being through non-specific influences on neurodevelopmental processes. However, studies directly examining these pathways are scarce and only show limited effects<sup>46,52,89</sup>. This may be partly because current polygenic scores capture only small proportions of the heritability of these complex traits.

We further propose that while genetic and biological factors exert foundational influences, creating a latent vulnerability–resilience spectrum<sup>90</sup>, environmental exposures and life experiences have crucial roles in shaping ill-being and well-being, often exerting distinct effects. Specifically, some psychosocial factors may act as broad modulators and influence a wide range of mental health outcomes (for example, neuroticism exacerbating ill-being while simultaneously suppressing well-being), whereas other factors exert more differentiated effects (for example, extraversion amplifying well-being more than it mitigates ill-being). Similarly, at the societal level, sociodemographic factors, cultural norms and policy changes may have either broad or domain-specific effects along the ill-being–well-being spectrum. For example, while economic hardship seems to be associated with both

distress and reduced well-being<sup>91</sup>, some global stressors, such as the COVID-19 pandemic, may increase ill-being without necessarily causing a proportional decline in well-being<sup>76,77</sup>.

Moreover, the multilevel influences on and experiences of mental ill-being and well-being are not static but evolve together over time. We therefore propose a life-course model of their development, as illustrated in Fig. 2. Across the lifespan, personal life events (for example, parental divorce), individual choices (for example, starting therapy), policy changes (for example, school reform) and societal disruptions (for example, the COVID-19 pandemic) can shape trajectories of ill-being and well-being in distinct ways. This model can be integrated with the wellbeing-illbeing structural model<sup>92,93</sup>, which conceptualizes well-being and ill-being as dynamic experiences shaped by goal-related processes. According to the wellbeing-illbeing structural model, individuals may experience well-staying, characterized by the presence of an achieved goal state, or well-moving, reflecting progress towards a desired goal. Conversely, ill-being can manifest as ill-moving, where perceived threats or challenges signal a risk of losing valued goals, or ill-staying, which arises when a goal state is lost. These temporal processes of influences and experiences underscore the need for longitudinal approaches to examine how stability and change in exposures interact with positive and negative mental health development. Future research should use longitudinal causal modelling to determine, for example, whether ill-being serves as a causal risk factor for reduced well-being. By considering multilevel interactions and their temporal patterns, these frameworks advance beyond previous models, offering a road map for research and interventions that recognizes the context-sensitive, dynamic nature of mental health.

Insights from our multilevel framework on the relationship between ill-being and well-being may have important implications for policy and intervention. The framework emphasizes the potential for environmental and societal factors to moderate risk and promote well-being, underscoring the need for policies that create supportive social environments. Strong family support systems and high-quality educational environments can serve as protective buffers against non-specific genetic and biological vulnerabilities. Moreover, recognizing that well-being is more than the mere absence of ill-being suggests that interventions should go beyond symptom reduction. Interventions and policies should therefore not only alleviate distress but also actively promote positive mental health.

Our review also highlights key limitations in existing research on the nature of the relationship between mental ill-being and well-being. A major challenge at many levels of analysis is that ill-being and well-being are rarely examined as distinct constructs within the same study. Instead, most studies have examined either ill-being or well-being separately or have incorporated aspects of one construct within the other. Conclusions regarding their shared and unique determinants, predictors, mechanisms and outcomes are thus largely based on comparisons of findings across studies that use different constructs, measures and samples, limiting the ability to assess their interrelatedness. Future research should seek to simultaneously assess both negative and positive aspects of mental health<sup>94</sup> and use rigorous modelling approaches to examine their structure and interdependencies. For example, hierarchical models, capable of capturing both global and subdomain dimensions of mental ill-being<sup>6,7</sup> and well-being<sup>15</sup>, can be used to investigate their shared and distinct causes and consequences. However, such studies face methodological challenges due to inconsistencies in measurement. Widely used instruments, often developed in the Western world, vary greatly in content and scope. For example, a content analysis of 7 widely used depression scales identified 52 disparate symptoms and low overlap across scales<sup>95</sup>. Similarly, well-being measurements differ substantially across studies, with large variations in conceptual approaches<sup>10</sup>, undermining replicability and cross-study inferences. Addressing these limitations through standardized assessments and harmonized methodologies

will be critical for advancing research on the interplay between ill-being and well-being.

In the era of big data, another challenge is that many results derive from a limited number of large-scale volunteer datasets, raising concerns about generalizability. Although these datasets are of immense scientific value, they predominantly comprise individuals of European descent and higher socio-economic status, failing to adequately represent global populations<sup>96</sup>. This considerable over-representation of affluent Western societies is concerning, given distinctively different conceptualizations of well-being held in these societies than in other world regions<sup>97</sup>. Affluent Western societies tend to idealize attaining maximum levels of happiness to a greater extent than other societies, which may affect the generalizability of associations between ill-being and well-being worldwide<sup>97</sup>. Furthermore, several groups are consistently under-represented in widely used large-scale samples, including immigrants and refugees, older individuals, homeless people, LGBTQ+ individuals and mental health inpatients. While studies using self-report scales or clinical interviews of patients with mental illness largely support the dual-continuum model of ill-being and well-being, results from the few studies with patients with severe mental illness instead indicate that these constructs are highly negatively correlated<sup>22</sup>. Future studies using large-scale datasets should transparently report sample characteristics and interpret findings within their demographic and cultural contexts<sup>96</sup>. Moreover, to improve generalizability and examine contextual variation, both funding agencies and researchers should prioritize data collection from under-represented populations and world regions. Strategies such as targeted sampling approaches and community collaborations can help to improve diversity in research participation. A balanced approach is also essential, drawing on the strengths of both big-data studies and smaller, investigator-led studies with tailored research designs and greater phenotypic depth<sup>98</sup>.

The rapid development of technology, the climate crisis and ongoing global economic and sociopolitical changes underscore the urgent need to examine how emerging factors shape mental ill-being and well-being and their interrelationship. In recent decades, the pervasive use of social media and artificial intelligence has become part of our daily lives, with far-reaching implications for social interactions and mental health<sup>99,100</sup>. Meanwhile, climate change disrupts both the physical environment and societies, acting as a risk amplifier by deteriorating conditions for good mental health and exacerbating inequalities<sup>101</sup>. Economic inequality is now recognized as a key challenge to nations' and individuals' health and well-being<sup>102</sup> and intersects with sociopolitical polarization, which further contributes to mental health risks<sup>103</sup>. To better understand the implications of these societal shifts for mental ill-being and well-being, future research must adopt interdisciplinary approaches and leverage large-scale datasets, including longitudinal registries, social media analytics and environmental monitoring systems. These approaches should be complemented by experimental designs examining causality and mechanisms and qualitative research that provides richer contextual insights. Such research will help to uncover new insights into the nature of the relationship between ill-being and well-being, ultimately informing targeted interventions and policy recommendations.

In conclusion, our interdisciplinary review and synthesis provides evidence for a differentiated perspective, suggesting that the relationship between mental ill-being and well-being varies across levels of analysis. Genetic influences and biological substrates show substantial overlap, suggesting they function as broad, non-specific determinants and mechanisms. By contrast, environmental influences, life experiences and societal events often exert divergent effects. To deepen our understanding of the multilayered relationships between mental ill-being and well-being, future research should incorporate subdomain-specific concepts for greater granularity and examine lifespan dynamics to capture their complex interconnectedness in a rapidly changing world.



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## Author contributions

C.K.T., M.B., M.E., R.B.N., M.B.P., E.Y., R. Chegeni, E.R. and T.v.S. conceptualized the project. C.K.T., M.B., M.E., R.B.N., M.B.P., E.Y., E.R. and T.v.S. wrote the original manuscript. E.R.A., S.N.A., H.A., Z.A., T.B., D.B., E.J.B., L.D.B., O.D.B., M.G.N.B., A.C., R. Cheesman, R. Chegeni, L.C.-G., P.A.D., J.C.E., M.E., N.H.E., E.M.E., Y.F., L.F., S.F., S.H.F., E.F., L.G., K.G., T.H., L.S.H., V.K., M.K., K.G.K., J.L., T.H.L., N.M., H.H.M.M., L.M., T.A.M., T.E.M., N.N., T.S.N., L.B.N., E.N., A.O., W.P., Q.Q., R.R.-C., V.S., D.S., O.M.S., A.D.T., I.J.E.T., F.A.T., S.T., V.S.U. and E.G.V. provided comprehensive feedback on the manuscript. C.K.T. and T.v.S. produced the figures. All authors reviewed and approved the final manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

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