Review article

The human physiology of well-being: A systematic review on the association between neurotransmitters, hormones, inflammatory markers, the microbiome and well-being

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ABSTRACT

To understand the pathways through which well-being contributes to health, we performed a systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines on the association between well-being and physiological markers in four categories, neurotransmitters, hormones, inflammatory markers, and microbiome. We identified 91 studies. Neurotransmitter studies (Knumber of studies=9) reported only a possible positive association between serotonin and well-being. For the hormone studies (K = 48), a lower momentary cortisol level was related to higher well-being (meta-analytic r = −0.06), and a steeper diurnal slope of cortisol levels. Inflammatory marker studies (K = 36) reported negative or non-significant relations with well-being, with meta-analytic estimates of respectively r = −0.07 and r = −0.05 for C-reactive protein and interleukin-6. Microbiome studies (K = 4) reported inconsistent associations between different bacteria abundance and well-being. The results indicate possible but small roles of serotonin, cortisol, and inflammatory markers in explaining differences in well-being. The inconsistent and limited results for other markers and microbiome require further research. Future directions for a complete picture of the physiological factors underlying well-being are proposed.

1. Introduction

Mental health is defined by the World Health Organization as “a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively, and is able to make a contribution to his or her community” (World Health Organization, 2005). As such, mental health is more than the absence of mental disorders and includes the concept of well-being. Well-being is defined by the OECD as good mental states, including all of the various evaluations, positive and negative, that people make of their lives, and the affective reactions of people to their experiences (OECD, 2013). In line with these definitions of mental health and well-being, the attention and interest for well-being and happiness has increased a lot in the past 20 years with a growing number of scientific publications every year in different disciplines (see the review of Kim et al., 2018). Besides being a protective factor associated with overall physical and mental health (Blener et al., 2017; Greenspoon and Saklofske, 2001), the positive effects of well-being are found to be independent from the negative effects of ill-being, such as depression, indicating the importance of investigating well-being (Howell et al., 2007). In addition, well-being is related to various positive life outcomes and functioning, such as a long, healthy life (James et al., 2017; Kim et al., 2019; Steptoe, 2019; Zaninotto and Steptoe, 2019), educational achievement, happy marriage, and productivity at work (Chapman and Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015).

The findings of behavioral and molecular genetics studies indicate a substantial role of biological and physiological factors underlying differences in well-being. Twin studies have estimated the heritability of well-being, i.e., the genetic contribution to the variation in well-being, to be around 40% (Bartels, 2015; Nes and Ryxsamb, 2015; van de Weijer et al., 2020). Recently, three genome-wide association studies (GWAS) related specific genetic variants to well-being (Baselmans et al., 2019a; Okbay et al., 2016; Turley et al., 2018), with the latest GWAS reporting 148 and 191 associations for life satisfaction and positive affect, respectively. Follow-up analyses found evidence for enrichment of genes differentially expressed in the subiculum (part of the...
hippocampus) and enrichment for GABAergic interneurons to be related to the well-being spectrum (Baselmans et al., 2019a). These genetic results provide suggestions and starting points for the physiology of well-being, but a systematic overview of the research to physiological measures is currently missing.

In contrast to the large body of evidence on the relation between different human physiological factors, for example inflammatory markers and hormones, and ill-being (e.g., Dowlati et al., 2010; Knorr et al., 2010), the association with well-being is investigated less. However, it is hypothesized that well-being is associated with functioning of multiple physiological systems. To understand the pathways through which well-being might contribute to health and to enhance the development of future (more precise) mental health prevention and intervention strategies, it is crucial to better understand the association between physiological factors and well-being.

The goal of this paper is to systematically review the available studies on the association between physiological markers in four categories, namely neurotransmitters, hormones, inflammation, and the microbiome, and well-being. First, we briefly describe the definitions of well-being and the different categories of physiological markers studied in relation to well-being. Next, we describe the systematic review strategy and its outcomes, and finally we discuss the results and future directions.

1.1. Well-being

While there are multiple definitions and conceptualizations of well-being in the current psychological literature (Lambert et al., 2015), a distinction is often made between hedonic/subjective well-being and eudaimonic/psychological well-being (Ryan and Deci, 2001). The subjective well-being theory has been associated with hedonistic philosophical ideas on well-being (Lambert et al., 2015; Ryan and Deci, 2001). This philosophical definition of hedonism includes maximizing pleasure and minimizing pain as the ultimate goal of life. Modern-day subjective well-being measures therefore focus on levels of positive affect and negative affect and subjective satisfaction with life (Diener et al., 2018). The psychological well-being has emerged from eudaimonic philosophical theories (Lambert et al., 2015; Ryan and Deci, 2001). The eudaimonic philosophical theory extends beyond pleasure and pain only, and emphasizes living a virtuous life. Based on this idea, current psychological well-being measures include measures of positive functioning, thriving, and judgments about the meaning and purpose of an individual’s life (Ryff, 1989).

The WHO definition of mental health mentioned before mostly focuses on the eudaimonic well-being concepts like realizing abilities and well-being, and well-being, mainly distinguishing between hedonic and eudaimonic well-being.

1.2. Neurotransmitters

Neurotransmitters are chemicals in the nervous system that transmit messages between neurons, between neurons and muscles, or influence the electrochemical state of other cells (see Snyder and Ferris, 2000 for a review). Neurotransmitters have their primary functions within the central nervous system (CNS), but are present throughout the body and in several biological fluids, such as blood, plasma, cerebral spinal fluid (CSF), saliva, and urine. Neurotransmitters can be classified in two types, small molecule (classic) transmitters and neuropeptides. Small-molecule transmitters, like dopamine and serotonin, have quick direct effects on near cells. Neuropeptides, like oxytocin, have more subtle effects and can have more distant effects in the body.

Neurotransmitters are transported from the central nervous system to the periphery, via the blood–brain barrier and after filtration by the kidneys excreted in urine. In human research, levels of neurotransmitters are usually assessed in blood or urinary samples. Yet, it is not clear what blood plasma and urine measures of neurotransmitters reflect. Neurotransmitter levels from urinary samples are not seen as a reliable indicator of CNS activity, but is suggested to reflect changes in the peripheral autonomic system (Ailts et al., 2007). However, both human and animal studies suggest at least a positive correlation between neurotransmitter levels in the brain and the rest of the body (Marc et al., 2011).

Neurotransmitters are important for human mental and physical health and abnormalities in their levels or activity can lead to mental disorders. For example, serotonin has found to be important for mood, movement, pain, and the sleep-wake cycle and is implicated in various psychiatric and brain disorders, such as depression, and obsessive-compulsive disorders (Blows, 2000). Norepinephrine and epinephrine have mostly been related to arousal and the level of activity within a person. Dopamine has been associated mainly with movement, reward (learning), and addictions. Decreased dopamine levels have been related to increased anhedonia or emotional apathy as well (Bressan and Crippa, 2005). Furthermore, increasing dopamine levels using levodopa subsequently increased happiness in an economic decision game (Rutledge et al., 2015).

These associations suggest the involvement of neurotransmitters in well-being as well. However, the detection of levels of neurotransmitters in humans is challenging due to the short term effects, low levels in the brain, and their mixture with other molecules (Niyonambaza et al., 2019). Therefore, research on well-being and neurotransmitters is scarce and a systematic review can help to identify areas for future research.

1.3. Hormones

Hormones are chemical messengers produced in the endocrine glands and released into the blood stream to organs and tissues of the body to control or regulate different physiological processes, including growth, metabolism, and reproduction (Neave, 2007). Hormones are present throughout the body and in several biological fluids, such as blood, urine and saliva, but also in hair. Like neurotransmitters, hormones are messengers. However, the difference with neurotransmitters is the site of release, site of action, and speed of action. Hormones are produced in the endocrine glands, are secreted into the blood stream and act throughout the whole body, whereas neurotransmitters are produced and released in the central nervous system and more locally. Compared to neurotransmitters, the effects of hormones are slower and longer lasting and the hormone levels are easier to detect and measure in humans.

In a narrative review, Rector and Friedman (2018) discussed the state of the field of the association between well-being and hormones. Adrenal hormones, such as cortisol and DHEA(S) can cross the blood-brain barrier and can exert their influences on subjective experiences, such as well-being, directly via the brain. The most often studied hormone in relation to psychological experiences and well-being is cortisol (Rector and Friedman, 2018). A distinction can be made between the levels of cortisol, decline over the day (diurnal slope) and the cortisol response after waking up (the cortisol awakening response, aka CAR) (Chida and Steptoe, 2009; Fries et al., 2009). All cortisol measures have been linked to well-being in some studies, but inconsistent effects are present in the literature and a systematic review is currently missing.

In addition, the sex hormones testosterone and estrogen have been
associated with mood and well-being (e.g., Johnson et al., 2013; Wharton et al., 2012). For example, the fluctuations of estrogen levels in the menstrual cycle have been suggested to play a role in mood and affect fluctuations. Similarly, the levels and/or change in testosterone could be related to well-being, although recent studies report insignificant associations (Rector and Friedman, 2018).

In this systematic review, we review all available studies on different hormones and their association with well-being, taking into account the effect of the diversity of well-being measures. Furthermore, as hormone levels can differ across age and sex, we discuss these possible moderating effects on the association.

1.4. Inflammatory markers

The immune system is the body’s defence system against infections and diseases and consists of many biological structures and processes (Delves and Roori, 2000). Activation of the immune system and the resulting inflammatory response is related to an increased production of inflammatory markers such as interleukin (IL)-1β, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α and C-reactive protein (CRP). These cytokines are signaling molecules and act as chemical messengers to activate different parts of the cellular immune system response. The (baseline) levels of different cytokines have been related to different traits and behaviors. For example, CRP levels increase in response to acute stress, but people also differ in their baseline levels, i.e., depressed people show higher CRP levels (Khandaker et al., 2014; Osimo et al., 2019).

For well-being, in the large Whitehall study of nearly 3000 healthy middle-aged adults, negative associations between IL-6 and CRP and positive affect have been reported, but only in women (Steptoe et al., 2008). These associations were independent from age, BMI, and depressed mood. However, more recently, large studies to the association of levels of inflammatory markers and different well-being measures reported inconsistent effects, possibly depending on the sample and/or measure of well-being. For example, Fancourt and Steptoe (2020) reported only a small relation between CRP and self-realisation, and not positive affect and life satisfaction in a large sample of older adults (n~9000).

Recently, Jones and Graham-Engeland (2021) reviewed the association between inflammatory markers and positive affect and concludes that there is mixed support for the relation between the level of inflammatory markers and positive affect. In the current systematic review, we review the association of inflammatory markers with different measures of well-being and report on the moderating effects of age and sex.

1.5. Microbiome

The microbiome is defined as all the microorganisms, such as bacteria, fungi (e.g., yeasts and molds), protozoa (one-celled organisms) and viruses living on and inside the human body (Turnbaugh et al., 2007). The human gut microbiome is dominated by bacteria and each healthy person has a unique and relatively stable microbiota in their gut (Turnbaugh et al., 2007). It is estimated that more than 1000 species make up the diversity of the human gut microbial ecosystem (Blaut and Clavel, 2007; Siezen and Kleerebezem, 2011). The microbiome bacteria help to digest food, produce vitamins and control our physical health and immune system (Lloyd-Price et al., 2016; Nicholson et al., 2012). The microbiome composition can be measured non-invasively in humans, by extracting information about bacteria abundance and diversity from a fecal sample of participants.

More recently, researchers started to investigate the relation between the composition of the microbiome and mental health or complex traits, such as personality. Most research focused on depression and reported an association with an altered gut microbiota composition, i.e., reduced diversity (see for example Foster and McVey Neufeld, 2013; Neufeld et al., 2011; Winter et al., 2018). Personality traits, including neuroticism and sociability, have also been related to different abundances of different gut microbiome bacteria (Johnson, 2020). These findings suggest that the composition of the microbiome might play a role in well-being as well, and therefore we review the available literature.

2. Method

To bring together the literature on the association between the four physiological categories and well-being, four systematic reviews (for each category separately) were conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). The four categories we included were (1) neurotransmitters, (2) hormones, (3) inflammatory markers, and (4) the microbiome.

2.1. Information Source and Search Strategy

Until September 2th 2021, the search for relevant articles was conducted in the bibliographic databases PubMed and Web of Science. Additional articles that were missed during this search were identified via reference lists of the selected articles. The search strategy included combinations of search terms related to well-being and the search words of one of the other categories (see Table 1 for the full list of search). The search applied iterative combinations of these categories by employing the Boolean search operators AND (horizontal) and OR (vertical).

2.2. Study Selection and Data Extraction

Titles and abstracts of collected articles were screened for eligibility and were included if (1) an association between one of the physiological categories and a measure of well-being (i.e., not only the absence of depression) was investigated, (2) healthy, non-clinical human samples were included, (3) the studies were peer-reviewed, and (4) published in English. Articles were excluded when (1) the procedure included a mood or emotion induction procedure, (2) a clinical sample was included, (3) the papers were review papers or (4) descriptive planned studies.

In cases of insufficient information to determine eligibility, papers were subjected to further screening. The first author screened the full text reports and decided whether papers met the inclusion criteria. Uncertainties and disagreement were resolved through discussions with the other authors.

2.3. Meta-analysis and publication bias

If, after reviewing, a substantial number of studies were considered to be relatively homogeneous with respect to study design and reported effect, we meta-analyzed the reported associations using the Metafor package in R (R Core Team, 2017; Viechtbauer, 2010). For results to be included in the meta-analysis, a bivariate correlation (instead of a standardized regression or beta coefficient) had to be reported. Since we focus on bivariate correlations and standardized regression coefficients are often based on regression with different covariates, we did not include (transformed) standardized regression coefficients or other effect indices in the meta-analyses as this might lead to biased estimates (Roth et al., 2018). If bivariate correlations were not reported, study authors were contacted to ask for the missing data.

For normalization, correlations were transformed into Fisher Z scores, using the formula: $ES_e = 0.5 \times \log\left(\frac{1+r}{1-r}\right)$. After the meta-analysis, the estimate was transferred back to a correlation for reasons of interpretation, using $r = \frac{e^{2ES_e}}{1+e^{2ES_e}}$ (see Lipsey and Wilson, 2001).

As some studies used overlapping samples and most studies reported multiple associations and effect sizes, we applied a three-level meta-analysis (Van den Noortgate et al., 2014). This enabled us to include all
effect sizes while taking into account the dependency, by specifying three levels, (1) sampling variance of the effect sizes, (2) variance between effect sizes within studies using the same dataset, and (3) variance between studies.

As a potential moderator of the effect between the physiological measure and well-being, we included the type of well-being measure as a categorical variable (i.e., (1) positive affect (hedonic well-being), (2) life satisfaction (hedonic well-being) and (3) eudaimonic well-being measures). Furthermore, we tested the moderation by average age of the sample (continuous variable) and percentage of females in the sample (continuous variable).

To assess the possible presence of a publication bias, we plotted the distribution of the effect sizes in a funnel plot and applied the Egger’s test to test the significance of the asymmetry of the funnel plot (Egger et al., 1997). If the plot is too asymmetrical and the test significant, a publication bias can be expected.

3. Results

3.1. Study selection

Across the four categories, the initial electronic database searches resulted in almost 12,000 hits in PubMed and Web of Science. We summarized the selection progress in PRISMA Flow diagrams (see Fig. 1). By removing the duplicates and scanning the titles and abstracts of the remaining articles, a first selection was made based on the selection criteria. In addition, we included additional articles based on references. The selected articles were examined and read fully. Based on the full-text reading, 91 articles met our selection criteria and were included in our review. Note that some studies were included in multiple categories.

3.2. Neurotransmitters

Nine studies investigated the relation between different neurotransmitters and well-being (see Table 2 for the details).

3.2.1. Description of study designs and samples

The average number of participants across the studies is 193 (SD=311), with a range from 11 to 985. The average age of the included participants is 46.2 (SD=16.5, range=25–74) and the percentage included females is on average 57% (SD=39%) with a range from 0% to 100%. All studies were cross-sectional studies, correlating the levels of neurotransmitters to the well-being measures.
3.2.2. Neurotransmitter measures

Four studies (studies N1–4 in Table 2) included a measure of the urinary levels of epinephrine and norepinephrine. Four other studies (N5–8 in Table 2) investigated serotonin in relation to well-being in blood samples. Of these 4 studies, two (N5–6) assumed the serotoninergic functioning from the prolactin (PRL) response to fenfluramine. A lower PRL response is a marker of diminished serotonergic function.

Table 2

| No | Study                  | Neurotransmitter | Neuro sample | Sample N | Age M (SD) | % female | Design for NA | Control | WB measure | Relation WB          |
|----|------------------------|------------------|--------------|----------|------------|-----------|---------------|---------|-------------|----------------------|
| N1 | (Lindfors and Lundberg, 2002) | epinephrine + norepinephrine | urine       | 23       | -          | 52%       | Cross-sectional | No      | Ryffs PWB E   | ns                   |
| N2 | (Ryff et al., 2006)    | epinephrine + norepinephrine | urine       | 135      | 74 (7.1)   | 100%      | Cross-sectional | No      | Ryffs PWB E, PANAS H | positive relations epinephrine: $r = 0.20^*$, $p < .05$; norepinephrine: $r = 0.21^*$, $p < .05$ |
| N3 | (Zilioli et al., 2015b) | epinephrine + norepinephrine | urine       | 985      | 46.1 (11.7) | 56%       | Cross-sectional | No      | Ryffs PWB E   | ns                   |
| N4 | (Dos Santos et al., 2019) | epinephrine + norepinephrine | urine       | 233      | -          | 57%       | Cross-sectional | No      | Positive affect H | ns                   |
| N5 | (Zalda and Depue, 2001) | serotonin/ prolactin | blood       | 34       | 25 (3.1)   | 0%        | Cross-sectional | No      | PANAS H       | $r = -0.49^*$, $p = 0.005$ |
| N6 | (Flory et al., 2004)   | serotonin/ prolactin | blood       | 254      | 45 (3.1)   | 47%       | Cross-sectional | Yes     | Happiness H  | $\beta = 0.14^*$, $p = .007$ |
| N7 | (Duffy et al., 2006)   | serotonin         | blood       | 39       | 60 (5.1)   | 100%      | Cross-sectional | No      | PANAS H       | $r = .35$, $p = .03$ |
| N8 | (Williams et al., 2006) | serotonin         | blood       | 23       | 22 (5)     | 0%        | Cross-sectional | No      | PANAS H       | $\beta = 8.2^*$, $p = .002$ |
| N9 | (Toledo et al., 2019)  | β-endorphin       | blood       | 11       | 41.6 (11.2) | 100%      | Cross-sectional | No      | Mood ratings H | $r = -.43$, $p = .18$ |

Note. PANAS = Positive and Negative Affect Schedule, Ryff PWB = Ryff Scales of Psychological Well-Being.

* Although this is a longitudinal study, we reported the correlation at baseline, i.e., cross-sectional.

† Superscript H indicates a hedonic well-being measure, whereas E indicates a eudaimonic well-being measure.

3.2.3. Well-being measures

Seven studies (studies N2,N4–9 in Table 2) included a measure of positive affect or happiness and three studies included the Ryff’s Psychological well-being (PWB) scales (N1–3).

3.2.4. The association with well-being

Since we only identified a few studies per neurotransmitter, we could not perform meta-analyses, but provide a description of study results instead. Three of the four epinephrine and norepinephrine studies reported the absence of a cross-sectional relation between the blood levels of epinephrine or norepinephrine and positive affect or purpose in life (Dos Santos et al., 2019; Lindfors and Lundberg, 2002; Zilioli et al., 2015b, N1,N3,N4 in Table 2). Ryff et al. (2006) (N2) did report a positive association between the positive relations subscale of the PWB scale and epinephrine and between the autonomy scale and norepinephrine. Compared to the other studies, the sample of (Ryff et al., 2006) was older (mean age=74.0) and only included women, indicating a possible moderating effect of age on the association.

Regarding serotonin, the first PRL response study unexpectedly reported a negative association between serotoninergic functioning and positive affect in a small sample of men (n = 31) (Zalda and Depue, 2001, N5), indicating that lower serotoninergic functioning is related to higher positive affect. With a larger sample (n = 254, 47% female) and a similar design, Flory et al. (2004) (N6) reported a positive association between serotoninergic functioning and positive affect with no sex differences. This indicates that in both men and women a higher average positive mood was associated with a larger PRL response, i.e., better serotoninergic functioning. Furthermore, the relation between positive affect and serotonin was significant when controlling for negative affect, suggesting independent effects for positive affect and serotonin (Flory et al., 2004). In direct blood measures of serotonin, both Duffy et al. (2006) and Williams et al. (2006) (N7, N8) replicated the positive association between positive affect and serotonin levels in respectively a female and male sample. Overall, based on the limited number of available studies, higher positive affect is likely to be associated with higher levels of serotonin.

Lastly, levels of β-endorphin (β-END) in the blood were not related to a happy mood in the small sample (n = 11) of Toledo et al. (2019), N9 in Table 2).

3.2.5. Summary

To summarize, our systematic review revealed a possible association between serotonin and well-being. Serotonin levels were positively related to positive affect, i.e., hedonic well-being in three out of four studies. Furthermore, the effect was independent of negative affect in one study. The relation between serotonin and other measures of well-being, e.g., life satisfaction, quality of life or eudaimonic well-being measures has not been investigated so far. In studies with larger sample sizes, the moderation by age and sex should be investigated as well.

Levels of epinephrine and norepinephrine were mostly unrelated to measures of hedonic and eudaimonic well-being. Only in a sample of older women (age=74), there was a moderate positive correlation between subscales of the psychological well-being scale and (nor) epinephrine. More research to the moderating effects of the well-being measure, age and sex is needed to confirm the findings.

3.3. Hormones

The details and results of the 48 different studies on hormones in relationship to well-being are reported in Table 3 (cortisol) and Table 4 (other hormones).
3.3.1. Description of study designs and samples

The average number of participants in the studies is 608 (SD = 1542), with a range of 11–9127 participants. The average age is 40.1 (SD = 19.6, range = 13.9–80.3). The percentage included females is on average 59.5% (SD = 28.3%) with a range from 0% to 100%.

One study had an experimental design in which participants received oxytocin for 10 days and well-being levels were assessed (Barraza et al., 2013). Six studies were longitudinal studies, relating hormone levels to well-being a few years later or vice versa (Hou et al., 2015; Hoyt et al., 2015; Lackner et al., 2020; Stafford et al., 2017; Steptoe and Wardle, 2005; Wendsche et al., 2020). The remaining 41 studies were cross-sectional studies, of which 17 studies were experience sampling studies with multiple measurements of hormones and/or well-being per day or across days (see Tables 3 and 4).

3.3.2. Hormone measures

The hormones most often studied in relation to well-being are cortisol (k = 39) (see Table 3), dehydroepiandrosterone sulfate (DHEA-S; k = 7), testosterone (k = 4), vitamin D (k = 2), and estradiol (k = 2). Single studies looked at oxytocin, FSH, LH, prolactin (PRL), IGF-I and IGFBP-3 and thyroid-stimulating hormone (TSH) (see Table 4, ordered by hormone).

For cortisol, most studies used saliva samples to assess the cortisol level (k = 37), two studies used hair samples (Smyth et al., 2016; Wendsche et al., 2020), two studies blood samples (Sonnenblick et al., 2018; Toledo et al., 2019), and a single study used urine (Zilioli et al., 2015b). A distinction is made between the association of well-being with momentary levels of cortisol (k = 33), the cortisol awakening response (CAR) (k = 16), the diurnal response (k = 14), and the area under the curve (AUC) (k = 7) (see Table 3).

DHEA-S was measured in saliva (k = 3), blood (k = 3), or in urine (k = 1). Testosterone levels were mostly assessed in saliva (k = 3), whereas one study looked at the blood levels. Vitamin-D levels were assessed in the blood (k = 3). Estradiol was either assessed in blood or saliva. Finally, the levels of other hormones (FSH, LH, prolactin, IGFBP-3 and IGF-I) were assessed in blood (see Table 4).

3.3.3. Well-being measures

Positive affect items (k = 26), Satisfaction with Life scale (k = 8), the WHO-index in different forms (k = 7), and Ryff’s psychological well-being scale (k = 8) were mostly included in the studies. Other scales and items, such as the Subjective Happiness Scale, POMS and the Warwick Edinburgh Mental well-being scale were only included in single or a few studies (see Tables 3 and 4).

3.3.4. The association between well-being and cortisol

3.3.4.1. Cortisol level. The average or momentary level of cortisol was negatively related to well-being in 7 studies (CL2,3,5,9,10,17,21 in Table 3), whereas in 14 studies the relation did not reach significance. The studies with the largest sample sizes (respectively n = 2873 and n = 1657) reported significant, but small effects (studies C9, C17 in Table 3; Sin et al., 2017; Steptoe et al., 2008). Furthermore, 4 of the 8 studies (CL5,9,10, 17 vs CL1,6,7,8), that did control for negative affect or depression, including the two large studies mentioned before, reported a significant negative association between well-being and cortisol levels, suggesting independent effects for well-being.

Eight relatively homogeneous studies with 15 associations of salivary cortisol level and well-being could be included in a meta-analysis (CL3,4,7,8,11,12,16,17, see Fig. 2). One of these associations was provided by the authors. We excluded eleven studies due to reporting only a beta coefficient or not reporting effect sizes and nonresponse to our request for extra information. The remaining two excluded studies used blood samples.

Based on the included studies, the distribution of the effect sizes in the funnel plot appeared to be symmetrical and the Egger’s test was non-significant with Z = -2.40, p = .017, suggesting no publication bias. The meta-analysis resulted in an estimate of −.06 (SE = .03, 95%CI: −.11, −.001, t = −2.19, p = .046, r = −.06). This indicates a small negative association between momentary or average level of cortisol and well-being. The moderation by well-being measure (i.e., positive affect vs life satisfaction or eudaimonic well-being measures was not significant (p = −.08, SE = .010, p = .422 and p = −.16, SE = .010, p = .113). Age (β = .00, SE = .002, p = .736) and the percentage of females in the sample (β = .23, SE = .03, p = .472) were not significant moderators of the association.

Of the studies that specifically investigated morning levels of cortisol, one study reported a lower level of cortisol to be related to higher well-being (Sjogren et al., 2006; CM3), one study a higher level (Lindfors and Lundberg, 2002; CM2) and in the other 7 studies (CM1, CM4–9) the association did not reach significance.

Evening cortisol was negatively related to well-being in 3 out of the 4 studies in both adult and adolescent samples (Hoyt et al., 2015; Simpson et al., 2008; Stafford et al., 2017, CE2,3,4 in Table 3).

The two studies with hair cortisol concentration differed in their results. Wendsche et al. (2020) did not find a relation with well-being, whereas Smyth et al. (2016) did report a positive relation between hair cortisol and well-being, independent from negative affect, but only in the older adults (Mage = 78.6).

3.3.4.2. Cortisol awakening response. The reported effects and designs of the studies to the cortisol awakening response (CAR) differed a lot, therefore we could not perform a meta-analysis and we only describe the results. Sixteen studies investigated the CAR, with 12 of these not finding an association with different measures of well-being, including the studies with the largest sample sizes (n > 1500) (Sin et al., 2017; Stafford et al., 2017; Steptoe et al., 2008, CAR5,14,15 in Table 3). Two studies reported a negative relation, with a lower CAR related to higher scores on different well-being measures in an adult and adolescent sample respectively (Miller et al., 2016; Rickard et al., 2016, CAR11,12), whereas Pasquali et al. (2021), CAR16 reported a significant positive relation, with a higher CAR related to higher positivity in a small sample (n = 20). The last study found individual differences in the relation between well-being and the CAR response in healthy participants (Booij et al., 2016; CAR10 in Table 3).

3.3.4.3. Diurnal slope. Fourteen studies related the diurnal slope of cortisol (over the day) to well-being, with 4 studies reporting a non-significant association (CS3,4,8,14). Seven studies reported that a steeper slope (faster decrease of cortisol levels over the day after the CAR) was significantly related to higher well-being, i.e., positive affect or satisfaction with life (CS2,5,6,7,9,11,13) whereas two studies found a flatter slope related to higher well-being (CS1,12). Lastly, Booij et al. (2016), CS10 reported a significant relation between the diurnal slope of cortisol and well-being for the majority of their participants, but individual differences in the direction and strength. Suggesting an independent effect of well-being, of the five studies that did control for negative affect or depressive symptoms, four did find a significant association between a steeper diurnal slope of cortisol and well-being (CS2,7,9,12 in Table 3).

3.3.4.4. AUC. Seven studies looked at the total cortisol secretion captured in the area under the curve (AUC). Four reported no relation with well-being (AUC2,3,5,6). Small studies reported a positive (Pasquali et al., 2021, n = 20 participants, AUC7) or negative relation (Rickard et al., 2016, n = 47 participants, AUC4) with well-being. Finally, Smyth et al. (2015) (AUC1) showed total cortisol secretion is only significantly related to higher well-being when the participant is accurate in the time of sampling.
Table 3
Characteristics and results of the cortisol studies.

| No | Study | Sample | Sample N | Age M (SD) | % female | Design | Correct NA | WB measure | Result |
|----|-------|--------|----------|------------|----------|--------|------------|------------|--------|
| **Hair cortisol** | | | | | | | | | |
| HC1 | (Smyth et al., 2016) | hair | 88 young | 19.5 (2.2); 78.6 (6.7) | 100% | Cross-sectional | Yes | SHS<sup>HI</sup>, SWLS<sup>E</sup> and Ryffs PWB<sup>E</sup> | B<sub>HAIR</sub> = .060* |
| | | | 27 old | | | | | Only in elderly | |
| **Cortisol level** | | | | | | | | | |
| CL1 | (van Eck et al., 2016) | saliva | 87 | 42.1 | 0% | ESM | Yes | Positive affect<sup>H</sup> | no |
| CL2 | (Smyth et al., 1998) | saliva | 120 | 36.7 (12) | 71% | ESM | No | Positive affect<sup>H</sup> | -7, p < .05 |
| CL3 | (Lindfors and Lundberg, 2002) | saliva | 23 | - | 52% | Cross-sectional | No | Ryffs PWB<sup>E</sup> | Environmental mastery; r = -.56* |
| CL4 | (Polf et al., 2005) | saliva | 334 | 28.8 (10.4) | 75% | ESM | No | Positive affect<sup>H</sup> | r = -.012 |
| CL5 | (Steptoe et al., 2005) | saliva | 228 | 45-59 | 46% | ESM | Yes | Happiness<sup>H</sup> | -7*, p = .099 |
| CL6 | (Steptoe and Wardle, 2005) | saliva | 162 | 45-59 | 68% | Longitudinal | Yes | Happiness<sup>H</sup> | r = -.00005 |
| CL7 | (Evans et al., 2007) | saliva | 50 | 74.0 (7.0) | 68% | Cross-sectional | Yes | POS-GHQ<sup>H</sup> | r = -.03 |
| CL8 | (Jacobs et al., 2007) | saliva | 556 | 27 (8) | 100% | ESM | Yes | Positive affect<sup>H</sup> | r = -.00005 |
| CL9 | (Smyth et al., 2008) | saliva | 2873 | 50-74 | 73% | ESM | Yes | Positive affect<sup>H</sup> | Average: -7%* |
| CL10 | (Mathias et al., 2011) | saliva | 44 | 21 (3.4) | 100% | ESM | Yes | Positive affect<sup>H</sup> | moment: B = -.03* |
| CL11 | (Oishi et al., 2012) | saliva | 41/33/46 | - | 71% | ESM | No | SWLS<sup>H</sup>, POMS<sup>H</sup>, SWLS<sup>H</sup>, Meaning in life, Ryffs PWB<sup>E</sup> | r = -.08, -.29, -.01 |
| CL12 | (Petros et al., 2013) | saliva | 32 | 29 (5.7) | 63% | Cross-sectional | No | WHO WB index | r = -.01, -.30, -.01 |
| CL13 | (Smyth et al., 2015) | saliva | 49 | 20.5 (2.8) | 100% | ESM | No | Factor score: SHS<sup>E</sup>, SWLS<sup>E</sup>, PA<sup>E</sup>, Meaning in life, Ryffs PWB<sup>E</sup> | B<sub>HAIR</sub> = -.289 |
| CL14 | (Booij et al., 2016) | saliva | 30 (15 MDD 15 HCs) | 35 | 72% | ESM | No | Positive affect<sup>H</sup> | Average: β = -0.08 |
| CL15 | (Zimmaro et al., 2016) | saliva | 85 | 19.3 (1.4) | 69% | Cross-sectional | No | Ryffs PWB<sup>E</sup> | Daily mean: ns |
| CL16 | (Pauly et al., 2017) | saliva | 185 | 49 | 51% | ESM | No | Positive affect<sup>H</sup> | H arousal: r = -.08, L arousal: r = -.01 |
| CL17 | (Sin et al., 2017) | saliva | 1657 | 56.4 (12.1) | 57% | ESM | Yes | Positive affect<sup>H</sup> | B<sub>HAIR</sub> = -.065* |
| CL18 | (Smyth et al., 2018) | saliva | 115 | 41.23 (11.87) | 76% | ESM | No | SASI<sup>H</sup> | Moment: B = -.04* |
| CL19 | (Lackor et al., 2020) | saliva | 97 | 61.3 (10.0) | 0% | Longitudinal | No | SF-36, psychological WB<sup>E</sup> | B<sub>HAIR</sub> = -.121 |
| CL20 | (Srembrink et al., 2018) | blood | 60 | 56.7 (17.8) | 32% | Cross-sectional | No | POMS<sup>SE</sup>, VAS<sup>SE</sup>, WHO-5<sup>SE</sup> | ns |
| CL21 | (Toledo et al., 2019) | blood | 11 | 41.6 (11.2) | 100% | Cross-sectional | No | Mood items<sup>H</sup> | r = -.57* |
| **Morning** | CM1 | | | | | | | | |
| CM2 | (van Nierkerk et al., 2001) | saliva | 40 | 60-80 | 0% | Cross-sectional | No | Positive mood<sup>H</sup> | r = -.013 |
| CM3 | (Sjojren et al., 2006) | saliva | 257 | 30-64 | 50% | Cross-sectional | No | Ladder of life<sup>H</sup> | Environmental mastery: r = -.64* |
| CM4 | (Steptoe et al., 2007) | saliva | 72 | 33.6 (8.8) | 0% | ESM | Yes | PANAS<sup>H</sup> | β = -.19 |
| CM5 | (Daly et al., 2011) | saliva | 174 | 23 (5.7) | 66% | ESM | No | Positive affect<sup>H</sup> | B<sub>HAIR</sub> = .147 |
| CM6 | (Slatcher et al., 2015) | saliva | 1078 | - | 52% | Cross-sectional | No | Positive affect<sup>H</sup> | ns |
| CM7 | (Zilioli et al., 2015a) | saliva | 1325 | 55.6 (11.7) | 55% | Cross-sectional | Yes | SWLS<sup>H</sup> | β = -.02 |
| CM8 | (Stafford et al., 2017) | saliva | 7515 | - | - | Longitudinal | No | Warwick Edinburgh WB<sup>SE</sup> | β = -.02 |
| CM9 | (Zilioli et al., 2015b) | urine | 985 | 46.14 | 56% | Cross-sectional | No | Ryffs Purpose in life<sup>E</sup> | r = -.018 |

(continued on next page)
| No  | Study                                      | Sample | Sample N | Age M (SD) | % female | Design     | Correct NA | WB measure[^n] | Result  |
|-----|--------------------------------------------|--------|----------|------------|----------|------------|------------|----------------|---------|
|     |                                            | saliva |          |            |          |            |            |                |         |
|     |                                            | saliva | 40       | 60-80      | 0%       | Cross-sectional | No         | Positive mood[^H] | r = −0.08  |
|     |                                            | saliva | 41       | 61.8       | 56%      | ESM        | No         | PANAS[^H]      | r = −0.47^* |
|     |                                            | saliva | 315      | 17.1 (0.4) | 73%      | Longitudinal| Yes        | Positive affect[^H] | β = −.66^* |
|     |                                            | saliva | 1756     | -          | -        | Longitudinal| No         | Warwick Edinburgh WB[^H] | β = −.47^* |
|     | CAR1 (Lai et al., 2005)                    | saliva | 80       | 28.3 (8.0) | 52%      | Cross-sectional| Yes        | Chinese Affect Scale: Positive affect[^H] | ns       |
|     | CAR2 (Polk et al., 2005)                  | saliva | 334      | 28.8 (10.4)| 75%      | ESM        | No         | Positive affect[^H] | r = −0.08  |
|     | CAR3 (Evans et al., 2007)                 | saliva | 50       | 74.0 (7.0) | 68%      | Cross-sectional| Yes        | POS-GHQ[^H]   | F = 0.02  |
|     | CAR4 (Steptoe et al., 2007)               | saliva | 72       | 33.6 (8.8) | 0%       | ESM        | Yes        | PANAS[^H]      | β = −.32  |
|     | CAR5 (Steptoe et al., 2008)               | saliva | 2873     | 50-74      | 73%      | ESM        | Yes        | Positive affect[^H] | ns       |
|     | CAR6 (Hou et al., 2015)                   | saliva | 105      | 21.0 (1.2) | 55%      | Longitudinal| No         | Chinese Affect Scale: Positive affect[^H] | β = −.003 |
|     | CAR7 (Hoyt et al., 2015)                  | saliva | 315      | 17.1 (0.4) | 73%      | Longitudinal| Yes        | Positive affect[^H] | β = −.030 |
|     | CAR8 (Slatcher et al., 2015)              | saliva | 1078     | -          | 52%      | Cross-sectional| No         | Positive affect[^H] | β = −0.33^* |
|     | CAR9 (Ziloli et al., 2015)                | saliva | 1325     | 55.6 (11.7)| 55%      | Cross-sectional| Yes        | SWLS[^H]      | β = .019  |
|     | CAR10 (Booij et al., 2016)                | saliva | 30 (15 MDD 15 HC) | 35  | 72%      | ESM        | No         | Positive affect[^H] | indiv diff |
|     | CAR11 (Miller et al., 2016)               | saliva | 490      | 43         | 54%      | ESM        | No         | PANAS[^H]      | β = −.26^* |
|     | CAR12 (Rickard et al., 2016)              | saliva | 47       | 13.9 (7)   | 70%      | Cross-sectional| No         | Warwick-Edinburgh WB[^H] | r = −.43^* |
|     | CAR13 (Chong et al., 2017)                | saliva | 32       | 20.5 (2.3) | 53%      | Cross-sectional| No         | PANAS[^H]      | r = −.35^* |
|     | CAR14 (Sin et al., 2017)                  | saliva | 1657     | 56.4 (12.1)| 57%      | ESM        | Yes        | SWLS[^H]      | r = −.32  |
|     | CAR15 (Stafford et al., 2017)             | saliva | 1612     | -          | -        | Longitudinal| No         | SWLS[^H]      | r = −.17  |
|     | CAR16 (Pasquali et al., 2021)             | saliva | 20 (10 POS high, 10 POS low) | 21 (1.3) | 0%       | Cross-sectional| No         | Positive affect[^H] | Positive[^H] |
|     | Diurnal slope                             |        |          |            |          |            |            |                |         |
|     | CS1 (Ryff et al., 2006)                   | saliva | 135      | 74         | 100%     | Cross-sectional| No         | Ryffs-PWB[^H], PANAS[^H], MQS[^H] | 75 + subsample: r = .29^* steeper |
|     | CS2 (Lai et al., 2005)                    | saliva | 80       | 28.3 (8.0) | 52%      | Cross-sectional| Yes        | Chinese Affect Scale: Positive affect[^H] | ns       |
|     | CS3 (Polk et al., 2005)                   | saliva | 334      | 28.8 (10.4)| 75%      | ESM        | No         | Positive affect[^H] | r = −0.04  |
|     | CS4 (Steptoe et al., 2005)                | saliva | 228      | 45-59      | 46%      | ESM        | Yes        | Happiness[^H] | ns       |
|     | CS5 (Sjogren et al., 2006)                | saliva | 257      | 30-64      | 50%      | Cross-sectional| No         | Ladder of life[^H] | r = .16^* steeper |
|     | CS6 (Daly et al., 2011)                   | saliva | 174      | 23 (5.7)   | 66%      | ESM        | No         | Positive affect[^H] | B= −.02^* steeper |
|     | CS7 (Hoyt et al., 2015)                   | saliva | 315      | 17.1 (0.4) | 73%      | Longitudinal| Yes        | Positive affect[^H] | β = −.038^* steeper |
|     | CS8 (Slatcher et al., 2015)               | saliva | 1078     | -          | 52%      | Cross-sectional| No         | Positive affect[^H] | β = −.011^* steeper |
|     | CS9 (Ziloli et al., 2015a)                | saliva | 1325     | 55.6 (11.7)| 55%      | Cross-sectional| Yes        | SWLS[^H]      | β = −002^* steeper |
|     | CS10 (Booij et al., 2016)                 | saliva | 30 (15 MDD 15 HC) | 35  | 72%      | ESM        | No         | Positive affect[^H] | indiv diff |
|     | CS11 (Miller et al., 2016)                | saliva | 490      | 43         | 54%      | ESM        | No         | PANAS[^H]      | β = −.19^* steeper |
|     | CS12 (Sin et al., 2017)                   | saliva | 1657     | 56.4 (12.1)| 57%      | ESM        | Yes        | Positive affect[^H] | B= .012^* flatter |
|     | CS13 (Smyth et al., 2017)                 | saliva | 115      | 41.23 (11.87)| 76%      | ESM        | No         | SASS[^H]      | B= −.01^* |
|     | CS14 (Stafford et al., 2017)              | saliva | 6490     | -          | -        | Longitudinal| No         | Warwick Edinburgh WB[^H] | β = −.07  |

^H: Higher, ^*: p < 0.05, ^*: p < 0.01

(continued on next page)
and change in positive affect after exercise, but only in older men. One study found a positive relation between change of DHEA-S levels (Sonnenblick et al., 2018, H6).

3.3.5.1. DHEA-S. Dehydroepiandrosterone sulfate (DHEA-S) was not related to different measures of well-being in 6 of the 7 studies (H1–5,7). One study found a positive relation between change of DHEA-S levels and change in positive affect after exercise, but only in older men (Sonnenblick et al., 2018, H6).

3.3.5.2. Testosterone. Only one of the four studies on testosterone reported a positive correlation with quality of life in an elderly sample (\(M_{age} = 65\)) (Masuda et al., 2014). No relation between testosterone level and quality of life (Castanho et al., 2014), psychological well-being (Lacker et al., 2020), or positive affect was found (Martin and Ter-Petrosyan, 2019) in the other studies.

3.3.5.3. Vitamin-D. In a large sample of adolescents (\(n = 5066\), Schaeper et al. (2016) reported that higher levels of vitamin D (25(OH) D3) in blood were related to higher levels of well-being. This positive relation was replicated in a small sample of adults (\(n = 11\)) (Toledo et al., 2019).

3.3.5.4. Other hormones. Insulin-like growth factor-binding protein (IGFBP-3) and insulin-like growth factor (IGF-I) levels were respectively positively and negatively associated with the WHO-5 well-being index, but only in females (Emeny et al., 2014). Prolactin was negatively related to quality of life in males only, whereas estradiol, FSH and LH were not associated with quality of life in both males and females (Castanho et al., 2014). Finally, a 10-day oxytocin trial did not affect life satisfaction (Barraza et al., 2013).

3.3.5.5. Summary. To summarize, most studies that included blood level measures of DHEA-S and testosterone did not report a significant association with well-being, or only in a specific subsample. The finding of a positive relation between vitamin D and well-being was consistent, but as only two studies have been published on this relation, replication is needed. Furthermore, the single studies that investigated the association between other hormones and well-being reported mainly nonsignificant relations.

3.4. Inflammatory markers

Table 5 shows the details and results of the 36 studies on the association between markers of the inflammatory immune response and well-being.

3.4.1. Description of study designs and samples

The average number of participants in the studies is 1568 (\(SD = 2190\)), with a range of 11–8780 participants. The average age is 52.6 (SD = 13.7, range 20.5–77.4). The percentage included females is on average 59.1% (SD = 15.1) with a range from 29% to 100%. Thirty studies were cross-sectional studies, of which 5 studies were experience sampling studies with multiple measurements of inflammatory markers and/or well-being per day or across days. Six studies were longitudinal studies, relating well-being to hormone levels a few years later or vice versa (see Table 5).

3.4.2. Inflammatory markers

In the 36 studies, CRP (number of studies: \(k = 26\)), IL-6 (\(k = 25\)), fibrinogen (\(k = 7\)), other inflammatory cytokines (\(k = 7\)), a composite score of inflammatory markers (\(k = 3\)), and tumor necrosis factor (TNF) (\(k = 5\)) were included in relation to well-being. Single studies included...
Table 4
Characteristics and results of the other hormone studies.

| No | Hormone  | Study                                      | Sample | Sample N | Age M (SD) | % female | Design | Control | WB measure | Result       |
|----|----------|--------------------------------------------|--------|----------|------------|----------|--------|---------|------------|--------------|
| H1 | DHEA-S   | (van Niekerk et al., 2001)                 | saliva | 40       | 60.80     | 0%       | Cross-sectional | No         | Positive affect† | Morning: r = 0.13 Evening: r = −0.08 |
| H2 |         | (Petros et al., 2013)                     | saliva | 32       | 29        | 63%      | Cross-sectional | No         | WHO WB index  | r = −0.23 |
| H3 |         | (Pauly et al., 2017)                      | saliva | 185      | 49        | 51%      | ESM                | No         | Positive affect† | High arousal: r = −0.07 Low arousal: r = −0.06 |
| H4 |         | (Castanho et al., 2014)                   | blood  | 120      | 65.2      | (8.8)    | Cross-sectional | No         | WHOQOL-BREF3† | Males: β = −0.220 Females: β = −0.265 |
| H5 |         | (Yoo et al., 2016)                       | blood  | 1043     | 55.24     | 55%      | Cross-sectional | No         | Positive affect† | Japanese: β = −0.086 US: β = −0.009 |
| H6 |         | (Sonnenblick et al., 2018)                | blood  | 60       | 56.7      | (17.8)   | Cross-sectional | No         | POMS8, VAS11, WHO-51E | Change: r = .36 * Only older (r = .38 *) and males (r = .35 *). |
| H7 |         | (Zilidi et al., 2015b)                   | urine  | 985      | 46.1      | (11.7)   | Cross-sectional | No         | Ryff PWE Purpose in life† | r = −0.18 |
| H8 | Testosterone | (Masuda et al., 2014)          | saliva | 79       | 65.4      | (11.1)   | Cross-sectional | No         | WHO-QOL26† | Males > 65 years: r = .474 * Females: r = .432 * |
| H9 |         | (Martin and Ter-Petrosyan, 2019)          | saliva | 87       | 21.2      | (6.1)    | Cross-sectional | No         | PANAS‡ | r = −.14 |
| H10|         | (Lacker et al., 2020)                    | saliva | 97       | 61.3      | (10.0)   | Longitudinal   | No         | SF-36†, PWB scale† | b = 1.17 |
| H11|         | (Castanho et al., 2014)                  | blood  | 120      | 65.2      | (8.8)    | Cross-sectional | No         | WHOQOL-BREF3† | Males: β = −0.093 Females: β = −0.149 |
| H12| Estradiol | (Lacker et al., 2020)                    | saliva | 97       | 61.3      | (10.0)   | Longitudinal   | No         | SF-36†, PWB scale† | b = −1.01 * |
| H13|         | (Castanho et al., 2014)                  | blood  | 120      | 65.2      | (8.8)    | Cross-sectional | No         | WHOQOL-BREF3† | T and E2 ratio: b = 1.076 * |
| H14| Vitamin D | (Schaefer et al., 2016)                  | blood  | 5066     | 14.7      | 49%      | Cross-sectional | No         | Emotional WB† | Males: β = −0.114 Females: β = −0.106 |
| H15|         | (Toledo et al., 2019)                    | blood  | 11       | 41.6      | (11.2)   | Cross-sectional | No         | Mood items† | Parent rating: E = 1.927 * |
| H16| Oxytocin | (Barraza et al., 2013)                   | intranasal OT | 39      | 80.3      | 38%      | Experimental  | No         | SWLS6, POMS6† | No effect of the oxytocin treatment (p > .05). |
| H17| FSH, LH, PRL | (Castanho et al., 2014)                | blood  | 120      | 65.2      | (8.8)    | Cross-sectional | No         | WHOQOL-BREF3† | Prolactin: males (β = −0.328 *), females (β = −0.009) |
|    |         |                                             |        |          |           |          |                |            |                | FSH: males (β = −0.44), females (β = −0.001) |
|    |         |                                             |        |          |           |          |                |            |                | LH: males (β = −0.042), females (β = −0.055) |
|    |         |                                             |        |          |           |          |                |            |                | women (β = .14 *), men (β = −10). |
|    |         |                                             |        |          |           |          |                |            |                | women (β = −.14 *), men (β = −.03) |

Note: WB= well-being, WHO= World Health Organization, PA= positive affect, WHOQOL = World Health Organization Quality of Life Instruments, POMS= Profile of mood states, VAS= Visual analogue mood scale, WHO-5 = World Health Organization well-being index, Ryff PWB= Ryff Scales of Psychological Well-Being, PANAS = Positive and Negative Affect Schedule, SF-36 = 36-Item Short Form Survey. †Superscript H indicates a hedonic well-being measure, ‡E indicates a eudaimonic well-being measure and H/E indicates a measure that includes both hedonic and eudaimonic concepts.

**Fig. 2.** Results of the meta-analysis on the correlation between momentary cortisol and well-being, based on 8 studies and 15 effect sizes.
| Immune marker | No | Study | Immune marker | Sample | Age M (SD) | % female | Design | Control | WB measure | Result |
|---------------|----|-------|---------------|--------|------------|----------|--------|---------|------------|--------|
| CRP           | CRP1 | (Steptoe et al., 2008) | blood | 2873 | 50.74 (3.6) | 73% | ESM | Yes | Positive affect[^1] | Women: OR = 0.53 |
|               | CRP2 | (Deverts et al., 2010) | blood | 2544 | 40.2 (16.4) | 52% | Longitudinal | Yes | CES-D: positive affect[^2] | b = −0.06[^*], only blacks |
|               | CRP3 | (Hamer and Chida, 2011) | blood | 797 | 52.1 (10.2) | 54% | Cross-sectional | Yes | SWLS[^5] | β = −0.24[^*] |
|               | CRP4 | (Carpenter et al., 2012) | blood | 92 | 30.5 (9.2) | 51% | Cross-sectional | No | QoL[^1] | r = −0.170 |
|               | CRP5 | (Friedman and Ryff, 2012) | blood | 998 | 58 (0.4) | 55% | Cross-sectional | Yes | Enjoyment Satisfaction[^5] | r = −0.154 |
|               | CRP6 | (Steptoe et al., 2012) | blood | 7795 | 65.6 (11.4) | 55% | Cross-sectional | Yes | SWLS[^5] | r = −0.07[^*] |
|               | CRP7 | (Rissanen et al., 2013) | blood | 305 | - | - | Longitudinal | No | QoL[^1], eudaimonic | r = 0.043 |
|               | CRP8 | (Nowakowski, 2014) | blood | 3005 | 69.3 (7.9) | 52% | Cross-sectional | No | Life satisfaction[^1] | OR = 0.90[^*], r = −0.08 |
|               | CRP9 | (Sin et al., 2015b) | blood | 872 | 57.9 (11.5) | 57% | Cross-sectional | No | General happiness[^11] | OR = 0.92[^*], r = −0.07 |
|               | CRP10| (Sin et al., 2015a) | blood | 969 | 58 (11.5) | 57% | Cross-sectional | Yes | Happiness[^11] | β = −0.02 |
|               | CRP11| (Zilioli et al., 2015b) | blood | 985 | 46.1 (11.7) | 56% | Cross-sectional | No | Life purpose: Ryff | nr |
|               | CRP12| (Marteinsson & et al., 2016) | blood | 944 | 45.9 (11.7) | 50% | Cross-sectional | No | QoL: ladder[^1] | β = −0.09 |
|               | CRP13| (Sturgeon et al., 2016) | blood | 688 | 53.9 (7.2) | 52% | Cross-sectional | No | PANAS[^9] | r = −0.094[^*] |
|               | CRP14| (Blevins et al., 2017) | blood | 3093 | 29 (1.8) | 51% | Cross-sectional | Yes | WHO-5[^5] | r = −0.092[^*] |
|               | CRP15| (Okeley et al., 2017) | blood | 5622 | 62 (11.1) | 50% | Longitudinal | Yes | Happiness[^11] | r = −0.01 |
|               | CRP16| (Graham-Engel et al., 2018) | blood | 220 | 46.2 (11.1) | 65% | ESM | No | QoL: CASP-19[^4] | risk = −29[^*], r = −0.08 |
|               | CRP17| (Ironson et al., 2018) | blood | 1979 | 51.9 (19.2) | 58% | Cross-sectional | Yes | PANAS[^9] | β = −0.025, r = −0.08 |
|               | CRP18| (Lin et al., 2018) | blood | 246 | 41.1 (12.2) | 43% | Cross-sectional | Yes | SWLS[^5] | r = −10[^*], ns after control depression |
|               | CRP19| (Ong et al., 2018) | blood | 175 | 53.4 (7.6) | 54% | Cross-sectional | Yes | PANAS[^5], PA items[^5] | r = −1.3 |
|               | CRP20| (Ichino et al., 2018) | blood | 94 | 56.2 (7.3) | 57% | Cross-sectional | No | SWLS[^5] | r = −0.23[^*] (male) |
|               | CRP21| (Beydoun et al., 2019) | blood | 1767/150 | 48 | 56% | Longitudinal | Yes | CES-D: positive affect[^1] | γ = 0.01/−0.005 |
|               | CRP22| (Dos Santos et al., 2019) | blood | 233 | - | 57% | Cross-sectional | No | Positive affect[^1] | ns |
|               | CRP23| (Tait et al., 2019) | blood | 268 | 77.4 (6.8) | 72% | Cross-sectional | Yes | SF-36 HR-QoL[^1] | β = −0.71, r = −0.12 |
|               | CRP24| (Deen et al., 2020) | blood | 5919 | 50 | 29% | Longitudinal | No | SWLS[^4] | r = −0.02 |
|               | CRP25| (Fancourt and Steptoe, 2020) | blood | 8780 | > 50 | 55% | Longitudinal | Yes | Positive affect[^1] | B = −0.002 |
|               | CRP26| (Slavish et al., 2019) | blood | 108 | 20.5 (1.5) | 60% | ESM | Yes | Self-realisation[^5] | B = −0.007[^*] |
| IL-6          | IL1  | (Linden et al., 2007) | blood | 18-49 = 53, 50-64 = 47, 65 + = 73 | 74 (7.1) | 100% | Cross-sectional | Yes | Ladder of life[^1] | r = 0.11, r = −0.19, r = −0.12 |
|               | IL2  | (Friedman et al., 2007) | blood | 135 | - | 66% | Cross-sectional | No | Ryff’s PWB[^8] | Positive relations: |
|               | IL3  | (Steptoe et al., 2008) | blood | 2873 | 50-74 | 73% | ESM | Yes | Positive affect[^1] | Women: r = −0.01 |
|               | IL4  | (Moroznik et al., 2010) | blood | 1028 | 58.0 (11.6) | 55% | Cross-sectional | No | Positive affect[^1] | r = −0.02 |

(continued on next page)
| Immune marker | No | Study | Immune sample | Sample | Age M (SD) | % female | Design | Control | WB measure[^1][^2] | Result |
|---------------|----|-------|---------------|--------|------------|----------|--------|---------|-------------------|--------|
| IL5 (Matsuoka et al., 2011) | blood | 160 | - | 52% | Cross-sectional | No | Purpose in life Self-acceptance | SIS[^3] | r = 0.04 | ns |
| IL6 (Friedman and Ryff, 2012) | blood | 998 | 58 (0.4) | 55% | Cross-sectional | Yes | SWLS[^4] | r = 0.06[^4] | PB: Purpose life[^2] | r = 0.09 |
| IL7 (Andreasson et al., 2013) | blood | 347 | - | 100% | Cross-sectional | No | Positive relationships[^E] | CES-D: positive affect[^4] | r = 0.03 | ns |
| IL8 (Eisenhofer and Segerström, 2013) | blood | 119/1082 | 71.1 | 55% | Cross-sectional | No | Positive affect[^B] | Psyh WB[^B] | r = 0.03 | ns |
| IL9 (miyamoto et al., 2013) | blood | 1044 / 382 | 55.2 | 55% | Cross-sectional | No | Life purpose Positive affect[^B] | Psyh WB[^B] | r = 0.01 (US) | ns |
| IL10 (Rissimau et al., 2013) | blood | 305 | - | 70% | Cross-sectional | No | QoL ladder[^B] | SAS[^2] | r = 0.02 (Japan) | ns |
| IL11 (Sin et al., 2015b) | blood | 872 | 57.9 | 57% | Cross-sectional | No | Positive affect[^B] | SAS[^2] | r = 0.07[^2] | ns |
| IL12 (Sin et al., 2015a) | blood | 969 | 58 | 57% | Cross-sectional | Yes | Positive affect[^B] | SAS[^2] | r = 0.02 | ns |
| IL13 (Stellar et al., 2015) | blood | 94/119 | 46.14 | 56% | Cross-sectional | No | Life purpose: Ryff Psych WB[^B] | SAS[^2] | r = 0.03 | ns |
| IL14 (Ziloli et al., 2015b) | blood | 985 | 45.69 | 50% | Cross-sectional | No | Life purpose: Ryff Psych WB[^B] | SAS[^2] | r = 0.03 | ns |
| IL15 (Martinsdottir et al., 2016) | blood | 944 | 46.14 | 56% | Cross-sectional | No | Life purpose: Ryff Psych WB[^B] | SAS[^2] | r = 0.03 | ns |
| IL16 (Sturgeon et al., 2016) | blood | 688 | 53.9 (7.2) | 52% | Cross-sectional | No | SAS[^2] | SAS[^2] | r = 0.09[1] | ns |
| IL17 (Graham-Engeland et al., 2018) | blood | 220 | 46.2 (11.1) | 65% | Cross-sectional | No | SAS[^2] | SAS[^2] | r = 0.15[^2] | ns |
| IL18 (Ung et al., 2018) | blood | 175 | 53.4 (7.6) | 54% | Cross-sectional | Yes | SAS[^2] | SAS[^2] | r = 0.19[^2] | ns |
| IL19 (Ichino et al., 2018) | blood | 94 | 56.2 (7.3) | - | Cross-sectional | No | SWLS[^4] | SWLS[^4] | r = 0.32 (male) | ns |
| IL20 (Beydoun et al., 2019) | blood | 1700/150 | 48 | 56% | Cross-sectional | No | CES-D: positive affect[^B] | SAS[^2] | r = 0.01 (female) | ns |
| IL21 (Dos Santos et al., 2019) | blood | 233 | - | 57% | Cross-sectional | No | Positive affect[^B] | SAS[^2] | r = 0.03 | ns |
| IL22 (Tait et al., 2019) | blood | 268 | 77.4 (6.8) | 72% | Cross-sectional | Yes | SF-36 HR-QoL[^1] | SWLS[^4] | r = 0.07[^1] | ns |
| IL23 (Toldeo et al., 2019) | blood | 11 | 41.6 (11.2) | 100% | Cross-sectional | No | Mood items[^1] | SAS[^2] | r = 0.06 | ns |
| IL24 (Deen et al., 2020) | blood | 5919 | 50 | 29% | Cross-sectional | Longitudinal | Emotion vitality SF36 | SAS[^2] | r = 0.03 | ns |
| IL25 (Slavish et al., 2019) | saliva | 108 | 20.5 (1.5) | 60% | ESM | Yes | SAS[^2] | SAS[^2] | risk = 0.93 | ns |

**Fibrinogen**

| No | Study | Immune sample | Sample | Age M (SD) | % female | Design | Control | WB measure[^1][^2] | Result |
|----|-------|---------------|--------|------------|----------|--------|---------|-------------------|--------|
| F1 (Steptoe et al., 2005) | blood | 228 | 45.59 | 46% | ESM | Yes | Happiness (1–5)[^2] | SWLS[^2] | r = 0.15[^2] | ns |
| F2 (Hummer and Ghida, 2011) | blood | 797 | 52.1 (16.8) | 54% | ESM | Yes | QoL[^1][^2] | SWLS[^2] | r = 0.24[^2] | ns |
| F3 (Steptoe et al., 2012) | blood | 7795 | 65.6 | 55% | ESM | Yes | QoL[^1][^2] | SWLS[^2] | r = 0.32[^2] | ns |
| F4 (Sin et al., 2015a) | blood | 969 | 58 (11.5) | 57% | Cross-sectional | Yes | QoL[^1][^2] | SWLS[^2] | r = 0.02[^2] (women) | ns |
| F5 (Okely et al., 2017) | blood | 5622 | 62 | 50% | Cross-sectional | Yes | SAS[^2] | SAS[^2] | r = 0.01 | ns |
| F6 (Ong et al., 2018) | blood | 175 | 53.4 (7.6) | 54% | ESM | Yes | SAS[^2] | SAS[^2] | r = 0.03 | ns |
| F7 (Pancroy and Steptoe, 2020) | blood | 8870 | > 50 | 55% | Longitudinal | Yes | Positive affect[^2] | SAS[^2] | r = 0.01 | ns |

**TNF-α**

| No | Study | Immune sample | Sample | Age M (SD) | % female | Design | Control | WB measure[^1][^2] | Result |
|----|-------|---------------|--------|------------|----------|--------|---------|-------------------|--------|
| TNF1 (Linden et al., 2007) | blood | 18–49 = 53, 50–64 = 47, 65+ = 73 | - | 66% | Cross-sectional | No | SIS[^2] | SAS[^2] | r = 0.04 | ns |
| TNF2 (Matsuoka et al., 2011) | blood | 160 | - | 52% | Cross-sectional | No | Life satisfaction[^2] | SAS[^2] | r = 0.01 | ns |
| TNF3 (Rissimau et al., 2013) | blood | 305 | - | 57% | Cross-sectional | No | adipose:life:139, | 0.043 | ns |
| TNF4 (Dos Santos et al., 2019) | blood | 233 | - | 57% | Cross-sectional | No | Life satisfaction[^2] | SAS[^2] | r = 0.03 | ns |
| TNF5 (Tait et al., 2019) | blood | 268 | 77.4 (6.8) | 72% | Cross-sectional | Yes | SF-36 HR-QoL[^1] | SWLS[^4] | r = 0.04 | ns |

**Composite interleukins**

| No | Study | Immune sample | Sample | Age M (SD) | % female | Design | Control | WB measure[^1][^2] | Result |
|----|-------|---------------|--------|------------|----------|--------|---------|-------------------|--------|
| IM1 (Ziloli et al., 2015b) | blood | 985 | 46.14 | 56% | Cross-sectional | No | Life purpose: Ryff Psych WB[^B] | SAS[^2] | r = 0.03 | ns |
| IM2 (Ziloli et al., 2015b) | blood | 220 | 46.14 | 56% | Cross-sectional | No | Life purpose: Ryff Psych WB[^B] | SAS[^2] | r = 0.03 | ns |
The number of white blood cells, and matrix metalloproteinase (MMP) – 9 (see Table 5, ordered by inflammatory marker).

### 3.4.3. Well-being measures

#### Positive affect items or the Positive and Negative Affect Schedule (PANAS) (k = 20), Satisfaction with Life scale (k = 7), Ryff’s psychological well-being scale (k = 5), and Quality of life (k = 4) were mostly included in the different studies as well-being measures. Other well-being scales and items, such as the WHO-index, Subjective Happiness Scale and mood items were only included in one or two studies (see Table 5).

#### 3.4.4. The association between C-reactive protein (CRP) and well-being

Fourteen studies reported a negative association of CRP with different well-being measures, whereas the other 12 studies did not report a significant relation. Nine studies with a significant association also controlled for negative affect or depressive symptoms, suggesting independent associations between CRP levels and well-being (CRP1,2,3,5,6,15,18,25,26).

Sixteen relatively homogeneous studies reporting 26 associations between CRP and well-being reported a correlation and were included in a meta-analysis (CRP4,5,7,8,9,12–21,23). Nine of these associations from six studies were provided by the author. We excluded 10 studies, since they reported only a beta coefficient, an odds ratio or relative risk or no effect size, and did not respond to our request for extra information. Based on the included studies, the distribution of the effect sizes in the funnel plot appeared to be symmetrical and the Egger’s test was non-significant with Z = −1.33 and p = 0.182, suggesting no publication bias.

The meta-analysis resulted in an estimate of −0.067 (SE = 0.01, 95%CI: −0.10, −0.04, t = −4.68, p < .001, r = −0.067) (see Fig. 3). This indicates a small negative relation between CRP and well-being. The moderation by well-being measure (i.e., positive affect vs life satisfaction or eudaimonic well-being measures) was not significant (β = −0.02, SE = 0.03, p = .545 and β = .03, SE = .03, p = .295). Age (β = .00, SE = .001, p = .846) and the percentage of females in the sample (β = .07, SE = .26, p = .777) were not significant moderators of the association.

#### 3.4.5. The association between well-being and Interleukin-6 (IL-6)

IL-6 was negatively related to different measures of well-being in 11 studies, whereas the other 14 studies reported no significant association with IL-6. The significant relations were mainly with positive affect, quality of life, and life satisfaction. Only three (IL2,3,6 in Table 5) of the seven studies that controlled for negative affect reported significant associations between IL-6 levels and well-being (IL2,3,6,12,18,22,25).

Sixteen studies with 35 associations between IL-6 and well-being reported a correlation and were included in a meta-analysis (IL1.4–6,11–15,20,22,23). Six of these associations from four studies were provided by the author. We excluded 9 studies since they reported only a beta coefficient, an odds ratio or relative risk or no effect size, and did not respond to our request for extra information. The distribution of the effect sizes in the funnel plot appeared to be symmetrical and the Egger’s test was non-significant with Z = −1.34 and p = 0.179, suggesting no publication bias.

The meta-analysis resulted in an estimate of −0.051 (SE = 0.01, 95%CI: −0.08, −0.03, t = −3.91, p = .001, r = −0.051) (see Fig. 4), and indicates a small negative relation between IL-6 and well-being. The moderation by well-being measure (positive affect vs life satisfaction or eudaimonic well-being measures) was not significant (β = −01, SE = .04, p = .914 and β = .00, SE = .03, p = .923). Age (β = −00, SE = .002, p = .152) and the percentage of females in the sample (β = .14, SE = .10, p = .174) were not significant moderators of the association.

#### 3.4.6. The association between other inflammatory markers and well-being

Fibrinogen was negatively related to different measures of well-being in three studies (F2,3,7 in Table 5), whereas the other four studies reported no association with well-being (F1,4,5,6). In the large study of Steptoe et al. (2012, F3) (n = 7795), there was a small effect
between fibrinogen levels and well-being, but only in women, suggesting a moderation of sex on this effect. Furthermore, the average age of the participants was above 50 in all 7 studies, limiting the possibility to find age effects on the association.

Five studies assessed TNF-α and only in a small subsample of 65+ years (n = 73 participants), Unden et al. (2007) (study TNF1 in Table 5) reported a significant association with quality of life, whereas in the other larger studies no effects were found. In single studies, a cytokine composite score or other cytokines such as IL-10, IL-1B, and IFN-γ were negatively related to well-being in specific subsamples (IM1, 4,8,9). The white blood cell count (WBC) was negatively associated with positive affect and self-relation, but not life satisfaction in the study by Fancourt and Steptoe (2020) (study IM11 in Table 5). Finally, one study looked at matrix metalloproteinase (MMP)—9, a collagen-degrading enzyme that is up-regulated in inflammation (Martensdottir et al., 2016, IM12). The negative relation with quality of life did not reach significance after adjusting for medical conditions and cardiovascular risk factors.

3.4.7. Summary
To summarize, consistent negative associations between the inflammatory markers CRP and IL-6 and well-being were reported. A meta-analysis on a subset of 16 studies confirmed the small negative association between CRP (r = −0.067) and IL-6 levels (r = −0.051) and well-being. The effect was not different for hedonic and eudaimonic well-being measures. Other inflammatory markers such as fibrinogen, and TNF-α were either negatively or non-significantly related to well-being, suggesting a possible negative relation between inflammatory markers and well-being in general. The results might indicate moderating effects of age and sex, as some associations were only found in specific subsamples.

3.5. Microbiome

Table 6 shows the details and results of the 4 studies on measures of the microbiome related to well-being.

3.5.1. Description of study designs and samples
In the four studies, the number of participants ranged widely from 3 to 1054 adults. The age of the samples differed as well, ranging from adolescents to 30 year olds and average ages of around 50 (see Table 6). All studies were cross-sectional studies, correlating measures of the gut microbiome to the well-being measures.

3.5.2. Microbiome measures
All four studies used a fecal sample to extract bacterial DNA. Bacterial DNA can be studied on different taxonomic classification levels, including the phylum level, and genus or species level. For example, the phylum Bacteroidetes consist of a variety of bacterial genera, such as the Prevotella and Parabacteroides bacteria. Similarly, the phylum Firmicutes includes the genera Roseburia, Coprococcus and Flavonifractor and many other genera (Giccarelli et al., 2006; Wakita et al., 2018).

3.5.3. Well-being measures
The well-being measures used in the four studies were all hedonic measure, i.e., a happiness rating from 1 to 10, the PANAS, Profile of Mood States (POMS) and the RAND-36 health-related quality of life survey including an emotional well-being measure.

3.5.4. The association with well-being
Li et al. (2016) performed a closed experimental (105 days) in a lunar like environment on three healthy adults with minimal interference on gut microbiota by other factors. Every two weeks, stool samples and answers on the POMS questionnaire were collected, resulting in a total of 17 samples. The results were reported on genera level (i.e., a taxonomic rank in the biological classification of bacteria). The relative abundance (percent composition relative to all bacteria) of the genera Roseburia, Phascolarctobacterium, Lachnospira, and Prevotella bacteria showed consistent positive correlations with positive mood, whereas Faecalibacterium, Parabacteroides, Bacteroides, and Anaerostipes were negatively correlated with positive mood. The Prevotella, Parabacteroides, and Bacteroides genera are part of the Bacteroides phylum, whereas the other genera are part of the Firmicutes phylum.

In a larger sample of adults, Valles-Colomer et al. (2019) reported consistent positive associations between the relative abundance of the genera Faecalibacterium and Coprococcus bacteria, both from the Firmicutes phylum, and emotional well-being.

In children and adolescents, Michels et al. (2019) reported a positive association between the relative abundance of the phylum Firmicutes and happiness. With respect to genera levels, this association was mainly in the genera Lachnospiraceae and Ruminococcaceae. The abundance of the phylum Bacteroidetes (mainly the order Bacteroidales) and Euryarchaeota was negatively associated with happiness. Furthermore, a higher Firmicutes/Bacteroidetes ratio and a higher Simpson index (i.e., more diversity) was related to higher happiness.

Finally, Lee et al. (2020) divided participants in two groups for who respectively the Bacteroides or Prevotella were more abundant. In the
Prevotella-dominant group, a greater diversity of the gut microbiome (Shannon index) was related to higher positive affect. Furthermore, in the total sample, the abundance of the genera Agathobaculum (Firmicutes phylum) and Collinsella (Actinobacteria phylum) were negatively related to positive affect, whereas a greater abundance of PAC001043_g (a novel genus in the Lachnospiraceae family, Firmicutes phylum) was associated with higher positive affect.

3.5.5. Summary

To summarize, although all four studies significantly related well-being to certain bacteria or diversity of the microbiome, more research in larger samples is needed to replicate the findings and have a clear picture of the association between the microbiome and well-being. With respect to genera, a consistent result based on three studies was the positive relation between the abundance of the genera Lachnospiraceae and well-being. Furthermore, two studies reported that measures of gut microbiome diversity were related to higher well-being.

4. Discussion

To understand observed differences in well-being between people in more detail, and in order to enhance the development of future mental health prevention and intervention strategies, it is essential to identify physiological markers related to well-being. Therefore, the goal of this systematic review was to bring together the available literature on physiological markers related to well-being in four categories, namely neurotransmitters, hormones, inflammatory markers, and the microbiome. The systematic review resulted in respectively 48 and 36 studies on the association of hormones or inflammatory markers and well-being, whereas only 9 and 4 studies examined the relation between neurotransmitters or the microbiome and well-being. We first summarize and discuss the findings per category. Next, we propose directions for future research based on our current results.

Table 6

| No  | Study                        | Microbiome sample | Sample N | Age M (SD) | % female | Design           | Control NA | Well-being measure H/E | Result                                |
|-----|------------------------------|-------------------|----------|------------|-----------|------------------|------------|------------------------|---------------------------------------|
| M1  | (Li et al., 2016)            | Bacterial DNA from fecal samples | 3        | 30 .67     | .67       | Cross-sectional | No         | POMS H/E               | + Roseburia, Phascolarctobacterium, Lachnospiraceae, Firmicutes, Bacteroides, and Anaerostipes, - Faecalibacterium, Parabacteroides, Bacteroides, and Anaerostipes, + Faecalibacterium (p = 0.21), Firmicutes (p = 0.31), Firmicutes/Bacteroides ratio (p = 0.22) and Simpson diversity (p = 0.21). - Euryarchaeota (p = -0.24), Proteobacteria (p = -0.22). |
| M2  | (Michels et al., 2019)       | Bacterial DNA from fecal samples | 93       | 8-16       | -         | Cross-sectional | No         | Happiness H/E          | + Cyanobacteria (p = 0.21), Firmicutes (p = 0.21), Firmicutes/Bacteroides ratio (p = 0.22) and Simpson diversity (p = 0.21). - Euryarchaeota (p = -0.24), Proteobacteria (p = -0.22). |
| M3  | (Valles-Colomer et al., 2019)| Bacterial DNA from fecal samples | 1054     | 50.9/57.9  | .55       | Cross-sectional | No         | RAND-36 QoL H/E       | + Faecalibacterium (b=0.14) and Coprooccus (b=0.10) |
| M4  | (Lee et al., 2020)           | Bacterial DNA from fecal samples | 83       | 48.9 (13.2) | 0.56      | Cross-sectional | No         | PANAS H/E              | + Shannon diversity (b=0.31), - Agathobaculum and Collinsella (b=-0.05), + PAC001043_g (Lachnospiraceae)(b=0.01) |

Note: POMS= Profile of Mood States, QoL= quality of life, PANAS = Positive and Negative Affect Schedule. H/E Superscript H indicates a hedonic well-being measure, whereas E indicates a eudaimonic well-being measure.
4.1. Neurotransmitters

Nine studies investigated the association between levels of different neurotransmitters and well-being, mainly focusing on (nor)epinephrine and serotonin. In contrast to our expectations, we did not find studies that related dopamine levels to well-being and only a few studies related to (nor)epinephrine and serotonin. Levels of epinephrine and norepinephrine were mostly unrelated to measures of psychological well-being and positive affect. Only in a sample of older women (mean age=74), there was a moderate positive correlation between (nor)epinephrine and subscales of Ryff’s psychological well-being scale. More research on the moderating effects of well-being measure, age and sex is needed to confirm these findings.

Serotonin levels were more consistently positively related to the hedonic well-being measure positive affect, but the effect sizes were small. The relation between serotonin and other measures of hedonic well-being, e.g., life satisfaction, or eudaimonic well-being has not been investigated so far. In studies with larger sample sizes the moderation by age and sex should also be investigated.

The results should be interpreted in light of the difficulties of measuring neurotransmitters levels in humans due to their short term effects, low levels in the brain, and their mixture with other molecules (Niyonambaza et al., 2019). Furthermore there is an ongoing discussion whether urine or blood plasma measures of neurotransmitters reflect brain activity (Ailts et al., 2007; Marc et al., 2011). The suggested positive correlation between neurotransmitter levels in the brain and the rest of the body, i.e., urine or blood (Marc et al., 2011) does suggest that the detected association between serotonin in the blood plasma and well-being indicates the involvement of serotonin resulting from brain activity in well-being.

Applying positron emission tomography (PET) and labeling neurotransmitters can help to identify the regional specificity in the brain of neurotransmitters associated with well-being. For example, in the field of anxiety, it has been found that neurotransmission in social anxiety disorder is characterized by an overactive serotonin system in the amygdala, caudate nucleus, putamen, hippocampus and anterior cingulate cortex (Frick et al., 2015). Similarly, PET studies can directly give insight in the association of well-being and functioning of neurotransmitters in specific brain regions.

Furthermore, there is a lot of development in new ways to assess serotonin in different tissues and with new techniques, such as real-time continuous monitoring (Si and Song, 2018; Su et al., 2020). This might enable researchers to assess the level of different neurotransmitters more easily in the future and replicate the possible involvement of serotonin in complex traits like well-being.

4.2. Hormones

The association of different hormones with well-being has been investigated more often compared to the neurotransmitter research, as hormones are currently easier to assess via, for example, saliva samples. Of the 48 hormone studies, 39 studies included one or more measures of cortisol. The meta-analysis on the association between the level of momentary cortisol and well-being resulted in a small negative effect, r = −.06, indicating that lower cortisol levels are related to higher levels of well-being. In addition, although a meta-analysis could not be performed, another relatively consistent finding was the association of a faster decrease of cortisol levels over the day (i.e., steeper slope) with higher well-being. The results of the relation between the cortisol awakening response and total cortisol secretion and well-being were less consistent. However, as reported by Smyth et al. (2015), the timing of cortisol sampling is important. In their study, only when the participants strictly adhered to the sampling protocol, lower cortisol awakening response was associated with higher well-being. Furthermore, as indicated by Booij et al. (2016), large individual differences in the relation between different measures of cortisol and well-being were present in their sample. This makes it difficult, if not impossible, to find consistent associations when averaging the relation within a large sample. In an earlier review, the inconsistency of findings regarding hormones and positive affects is also suggested to be due to the variability in samples, age, measures of well-being and timing (Dockray and Steptoe, 2010). Furthermore, as cortisol is “the stress hormone” and there is a clear negative association between stress and well-being (e.g., Schiffrin et al., 2009), stress might mediate the relation between diurnal cortisol and well-being and controlling for stress is needed in future studies.

Cortisol can be sampled in saliva, urine, or hair and the levels in the different samples reflect different processes. Whereas salivary and urinary cortisol reflect the real-time levels of cortisol, hair cortisol reflects the cortisol exposure over longer periods of time and is related to chronic stress (Russell et al., 2012). Cortisol measured in cortisol and urine versus hair is therefore not directly comparable. We identified two studies using a hair sample of cortisol and only one (Smyth et al., 2016) reported a small negative association with well-being in elderly participants. Research in larger samples is needed to examine the relation of hair cortisol (i.e., long-term cortisol exposure) and well-being.

To summarize, most measures of cortisol were not consistently related to well-being and individual differences could play a large role in the association. However, the small associations between momentary levels of cortisol and the slope of the cortisol decrease over the day and well-being were consistent. This effect was not different for hedonic and eudaimonic well-being. In future research, researchers need to be stricter on the timing of the cortisol sample and avoid variability, e.g., by using tube caps with time recording and strict instructions to the participants. In addition, focusing on the individual patterns instead of the average cortisol response or level across individuals is necessary to understand the relation between cortisol and well-being in more detail.

The association of other hormones with well-being were investigated in only a few studies and most of these studies did not report a (consistent) significant association, limiting the ability to draw conclusions. DHEA-S and testosterone were not related to different measures of well-being in respectively 5 of the 6 studies and 3 of the 4 studies. This might reflect a power issue, as most sample sizes of the discussed studies are small (n < 100) or the absence of a detectable association between the levels of these hormones and well-being. More promising is the positive relation between vitamin-D in the blood and well-being. However, since this is based on only two studies, more research is needed to confirm this association.

Whereas oxytocin has mainly been investigated in relation to positive social behavior, oxytocin is also suggested to play a role in different behaviors and traits related to well-being, such as emotional processing, trust and depressive behaviors (IsHak et al., 2011). However, surprisingly, the direct relation between oxytocin and well-being has only been investigated in a single study (Barraza et al., 2015). In a small sample (n=21) of older adults (M=80) no association could be reported. Future direct and powerful studies should shed more light on the hypothesized association between well-being and oxytocin.

Finally, most studies on the different hormone levels included relatively older samples (average age: 53.1, and in 6 of the 14 studies the average age is above 65). Since hormone production and levels are affected by age (Sternbach, 1998; Van Cauter et al., 1996), more research is needed to study the effects of age on the association between hormones and well-being in age diverse samples.

4.3. Inflammatory markers

The results of the 36 studies on the inflammatory markers and well-being showed more consistent results compared to the previous categories. CRP was negatively associated with well-being in 14 of the 26 studies and IL-6 was negatively associated with well-being in 11 of the 25 studies, whereas the other studies did not find a significant effect. Additionally, both CRP (r = −0.07) and IL-6 (r = −0.05) showed small but significant negative relations with well-being in a meta-analysis. Based on the available studies, the well-being measure was not a significant
moderator, suggesting that the inflammatory markers have an influence on overall well-being and not on specific aspects of hedonic or eudaimonic well-being.

Besides CRP and IL-6, fibrinogen was negatively related to well-being in three of the seven studies, and other inflammatory markers such as other interleukins or white blood cell count were either negatively related with well-being or non-significantly. Based on these results, a consistent pattern of negative associations between different inflammatory markers and well-being emerges. Lower levels of baseline inflammatory markers, i.e., reflecting less activation of the immune system, is linked to higher well-being. The non-significant findings can either be due to weaker designs or smaller samples, leading to lower power.

Similar to the hormone studies, the reviewed inflammatory marker studies included relatively older samples. The average age of the samples is 52.6 (SD=13.7) and in 17 of the 36 studies the average age is above 50, while in only two studies the average age is below 30 years. As some studies suggested moderation by age (e.g., Fancourt and Steptoe, 2020), more research is needed into the effects of age on the association between inflammation and well-being in younger and age diverse samples.

A next step in the research on inflammation and well-being is the direction of effect. The direction of effect between inflammation and mental ill-being, i.e., depression, appears to be bidirectional. Patients with inflammatory diseases have a higher likelihood to develop major depressive disorder and often individuals with major depression show increased inflammatory markers, and the levels decrease with the recovery from depression (e.g., Amodeo et al., 2018; Dahl et al., 2014). As well-being and mental ill-being are related but have independent effects on health and other outcomes, the direction of effect between inflammation and well-being should be investigated. Some longitudinal studies in this review showed significant associations between inflammatory markers and well-being a few years later, indicating a possible causal effect from inflammation to well-being.

4.4. Microbiome

Lastly, the composition and diversity of the gut microbiome in relation to well-being is a relatively new and fast developing research field. We could only identify four studies that related the gut microbiome diversity or composition to well-being. All studies reported significant results with the abundance of different bacteria or the diversity of the microbiome associated with higher hedonic well-being, i.e., positive affect or quality of life, indicating that it is likely that the microbiome plays a role in well-being. However, more research is needed to be confident about the specific associations between the microbiome composition and well-being, because one study only included 3 participants, different effects of different bacteria have been studied, and there might be a publication bias in that only studies with significant effects are published in this upcoming field.

Microbiome research is further complicated by the possible effects of variation in dietary habits and geography on the composition of the gut microbiota. Ideally, when investigating the microbiome, participants should be in a stable environment, keep a constant diet and living habit, and maintain a certain activity level. As this can be difficult in daily life, Li et al. (2016) minimized the possible confounding by other factors by investigating three participants that stayed 105 days in a closed human life support system with minimal interference, i.e., a laboratory that simulates a lunar-like environment. This study gave the first insights in the unconfounded relation between the gut microbiome and well-being. In future studies outside such a system, the possible confounding by diet, environment and activity should be taken into account.

Another point of discussion is the current sampling methods for gut microbiome. Tang et al. (2020) reviewed the methods and concluded that more precise sampling methods for the composition and diversity of the gut microbiome are needed. Current measures from fecal samples (and other non-invasive methods) are just a proxy for the composition of the gut microbiome. More precise sampling methods are needed to increase the reliability of the microbiome research and to replicate findings.

4.5. Future directions

In different categories consistent relationships between physiological markers and well-being (e.g., the hormone cortisol, and inflammatory markers CRP and IL-6) were reported. With respect to these effects, further research should be conducted to investigate the direction of the effect or possible moderators or confounders on the effect, as suggested above. In other categories, such as neurotransmitters and the microbiome, additional research is needed to get a complete picture of the role of these physiological markers in relation to well-being. Besides further research into the association of physiological markers related to well-being in the single categories, promising fields for future research include the integration or combination of multiple physiological categories in relation to well-being, the direction of causality, and innovative ways to measure and analyze physiological data.

4.5.1. Integration

A first observation based on the reviewed studies is that the findings of the different studies are diverse and not connected. Most studies investigated the relation between one physiological marker and well-being. Similar to the criticized candidate gene literature (i.e., investigating the association of a single or a few candidate genes with well-being, depression or other genetically complex phenotypes) in which results are mixed and do not seem to replicate (e.g., Border et al., 2019; Johnson et al., 2017; van de Weijer et al., 2022), the pick-and-choose strategy for physiological markers might have led to similar inconsistent results. Where the genome-wide association approach has been introduced to systematically search for genetic variants for complex traits, a similar data-driven approach should be used for future research into the physiology of well-being. Combining multiple physiological markers across the different categories, aka an multi-omics approach, could result in a more complete picture of the physiology underlying well-being.

Combining multiple physiological markers across the different categories could result in a more complete picture of the physiology underlying well-being. An example of combining data is multi-omics approaches, that combine and integrate multiple types of omics data, such as genomics, proteomics, transcriptomics, epigenomics, metabolomics, and microbiomics (Hasin et al., 2017). All the different processes influence each other and by combining these data, researchers can get a broader picture and a more comprehensive insight in the physiological markers and human biology underlying traits or diseases. To learn more about multi-omics, Worheide et al. (2021) and Subramanian et al. (2020) provide helpful overviews and different applications of this approach within the domain of mental ill-being, e.g., for aggressive behavior and psychiatric disorders, can be found (Hagenbeek et al., 2021; Korologou-Linden et al., 2021).

To understand the physiology underlying well-being, multi-omics approaches can also be applied to the combination of hormones, neurotransmitters, inflammatory markers, and the microbiome. For example, the stress hormone cortisol, and inflammation, the reaction of the immune system, are strongly linked (e.g., Adam et al., 2017; Morey et al., 2015). Furthermore, recent research reported an influence of the gut microbiome on mental health via the level of neurotransmitters (Liu et al., 2020). The gut microbiome can alter the levels of different neurotransmitter and this alteration of neurotransmitters influences mental health. Similarly, an interaction between three categories, namely the gut microbiome, the stress response, including cortisol, and immune system is suggested to play a role in depression, and anxiety (Peirce and Alvina, 2019). As we have shown that cortisol, different immune factors and possibly the microbiome are associated with...
well-being, investigating these factors at the same time might lead to a clearer picture about the relation between the human physiology and well-being. To conclude, for a complete overview of the physiological markers underlying well-being, combining measures of multiple physiological markers into a large well-being study is needed.

4.5.2. Direction of effect

As we reported consistent associations of (diurnal) cortisol and different inflammatory markers with well-being, a next step is to investigate the direction of the effect between the physiological marker and well-being. Can the association be explained by a causal relationship from the physiological marker to well-being, vice versa, in both directions or is the association explained by another factor? If the direction of causation is known, this can help to design interventions to enhance well-being or prevent poorer mental health. The reported associations in this review are only correlational and it is impossible to determine causality in cross-sectional observational studies. Causality analyses, such as longitudinal (intervention) studies and Mendelian Randomization can enable future researchers to investigate the direction of causality in this field.

Longitudinal studies in which either well-being or the level of physiological factors, such as hormones or neurotransmitters are observed over time, or manipulated (e.g., by triggering their response or substitution) can allow for causal interferences to be made. For example, in the experimental design of Barraza et al. (2013) half of the participants received oxytocin for 10 days and the other half a placebo. The levels of well-being were compared before and after the treatment. There was no effect of the treatment on well-being in both groups. However, if an increase in well-being the oxytocin group, but not the placebo group had been reported, this would be evidence for a causal relation between oxytocin and well-being. Similarly, the other way around, interventions that increase well-being can be used to investigate if well-being has a causal effect on various physiological factors. For example, a meta-analysis across 20 randomized control trials (RCT) reported that mindfulness mediation is associated with immune system processes involved in inflammation, and biological aging, i.e., mediation resulted in a decrease in CRP levels (Black and Slavich, 2016). Similarly, a recent meta-analysis on the effects of meditation interventions on cortisol levels reported that such interventions resulted in reduced cortisol levels, but only when assessed in blood compared to saliva and in people at risk for somatic illnesses (Koncz et al., 2021). As mindfulness and meditation have also been linked to increased well-being, these findings could indicate a causal link between well-being and different physiological factors. Future randomized control studies specific to well-being interventions or physiological manipulations are needed to confirm these hypotheses and investigate the direction of causation.

Another approach to study the direction of causation, that does not need longitudinal data or any intervention, is Mendelian Randomization (MR), which uses genetic variants to test the causal relationships between an exposure variable and outcome. MR relies on the natural, random assortment of genetic variants resulting in a random distribution of genetic variants in a population (Smith and Ebrahim, 2003). In short, if the assumptions are met and a genetic variant is associated both with the exposure (e.g., inflammatory marker levels) and the outcome (e.g., well-being), this would provide supportive evidence for a causal effect of the immune response on well-being. To learn more about Mendelian Randomization, see Gagliano Taliun and Evans (2021) and Smith and Ebrahim (2003) for an overview and guidelines. Different applications of this approach within the domain of mental ill-being with physiological factors can be found as well (e.g., Poletti et al. (2021); Wardenaar et al. (2021)).

Finally, results of animal studies can indicate possible causal effects of well-being and physiological factors. Although there are limitations in generalizing results from animal studies to human well-being, these results can be the starting point for research in humans and provide clues about the mechanisms and causality. Animal research has been helpful in health-related research areas, but is rare in the well-being field, largely because of the subjective nature of well-being. In the field of depression and stress, animal research on physiological factors has reported different causal mechanisms. For example, in rats, a microbiome transplantation from severely depressed patients to the rats induced depression-like behaviors, like anhedonia and anxiety-like behaviors (Kelly et al., 2016). Similarly, rodents that experienced more induced stress showed higher levels of inflammatory markers (Powell et al., 2013). These results could indicate a possible causal effect between well-being and different physiological factors and future animal research to well-being can be used to investigate causality and confirm these hypotheses.

4.5.3. Innovations and data-driven research

Related to innovations in the methods to measure physiological markers, e.g., real-time continuous monitoring (Si and Song, 2018; Su et al., 2020), there are also rapid developments in the approaches to collect and analyze (big) data. Using the developments in the artificial intelligence and machine learning fields, patterns can be detected in physiological data that we would not predict. These approaches enable us to focus more on data-driven research instead of hypothesis driven research (Scheel et al., 2020). For example, using a data driving approach, and applying machine learning, Poletti et al. (2021) could distinguish between unipolar and bipolar depression based on the plasma levels of 54 cytokines, chemokines and growth factors (i.e., the immune-inflammatory signature) of the participants. For more information about artificial intelligence and machine learning, see overview articles, e.g., Jordan and Mitchell (2015); Yann LeCun, Yoshua Bengio (2015). Different applications of this approach within the domain of mental ill-being with physiological factors can be found as well (e.g., Poletti et al. (2021); Wardenaar et al. (2021)).

4.6. Limitations

The low number of studies in some categories of this systematic review limits our ability to draw more firm conclusions about the association between the physiological factors and well-being and this highlights the need for more studies investigating the physiology of well-being. Furthermore, the low number of studies could indicate a possible publication bias, especially in the newer fields, if studies with nonsignificant findings are not published.

Another limitation, touched upon briefly in the results of the different categories, is that only a limited number of studies controlled for negative affect and depressive symptoms when investigating physiological factors in relation to well-being. Since well-being and ill-being are related (Baselmans et al., 2018; Okbay et al., 2016), controlling for ill-being when investigating the relation between physiological factors and well-being can help to disentangle the independent associations of physiological factors with well-being and ill-being.

A similar approach of controlling for confounding effects could be interesting for hedonic and eudaimonic well-being measures. Although hedonic and eudaimonic well-being measures are strongly correlated, they also capture slightly different parts of well-being. As proposed by Ryff et al. (2004) hedonic and eudaimonic well-being could have partly different neurobiological and physiological correlates. To learn more about the distinction between hedonic and eudaimonic well-being, future studies should include both measures and when examining the effects of hedonic well-being control for eudaimonic well-being and vice versa.

A quantitative meta-analysis on the association between cortisol levels, two inflammatory markers (CRP and IL-6), and well-being was possible due to a substantial number of homogenous study designs and reported effects. We only included studies that reported bivariate correlations, not including standardized regression coefficients and other effect sizes, since in many regression different covariates are added, leading to biased estimates when including the partial correlations between the markers and well-being. As a
4.7. Conclusion

This systematic review of 91 studies on the association between physiological markers across four categories and well-being showed that more research is needed to understand the physiological markers underlying well-being in certain categories. Relatively robust negative, but small associations between cortisol and inflammatory markers such as CRP and IL-6, and well-being were reported, indicating that lower cortisol levels and lower response of the immune system are associated with higher levels of well-being. In the meta-analyses, these associations were not moderated by the type of well-being measure, indicating an association with overall well-being.

Future directions include innovative ways to measure the physiological markers and analyze the data, to investigate multiple physiological markers across the different categories at the same time in relation to well-being, and to investigate the direction of causality between the physiological markers and well-being.

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Declarations of interest

None.

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104733.

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