

## Mitoception Via the Metabokine GDF15 And Human Health

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## **Abstract**

To survive and thrive, living organisms must monitor and regulate cell-level energy supply, demand, and transformation. They do so through a brain-directed interoceptive process we refer to as “metaboception.” Here, we describe a specific metaboceptive signaling cascade mediated by the metabokine/cytokine growth differentiation factor 15 (GDF15), which we name “mitoception.” Mitoception involves an afferent signaling arm initiated by the integrative stress response (ISR), and an efferent signaling arm that simultaneously promotes energy conservation and fuel mobilization. *Afferent* mitoceptive signaling is mediated by GDF15 released when cells face energy demand in excess of their energy transformation capacity, creating an “energy gap”. *Efferent* mitoceptive signaling arises when GDF15 receptors in the brainstem receive the signal and initiate psychological experiences including fatigue and anxiety, together with neuroendocrine stress responses. Mitoceptive outputs thus reprioritize systemic energy metabolism to promote allostasis, survival, and long-term health. The proposed GDF15-driven mitoception cascade makes predictions about modifiable processes that shape disease risk, mental health, mood, resilience, well-being, and aging.

**Keywords:** metaboception, bioenergetics, mitoception, GDF15, energetic pain, fatigue, anxiety, behaviors, stress-disease cascade

## Introduction

To coordinate the symphony of physiological systems and activities that keep us alive, physiologically regulated, and thriving, the brain relies on interoceptive signals, such as those of nociception<sup>1,2</sup> and immunoception<sup>3,4</sup>. Sensory signals arise from almost all tissues of the body, enabling animal brains to perceive and precisely locate threats to physical integrity such as pressure, heat, and tissue damage. Nociceptive signals are hard to ignore – directing attention and actions towards those that promote survival. Similarly, the activated immune system uses cytokines to “subjugate the brain” and produce optimal healing conditions and behaviors<sup>5</sup>. A general capacity for *interoception* – the brain’s modeling of the internal state of the body<sup>6</sup> – is key to health.

The most vital element of life is the *flow of energy*<sup>7</sup>. Without energy transformation, cellular and organismal life ends. In the same way that the brain constantly integrates afferent signals to coordinate the visceral organs, movements, and the features of lived experience to avoid physical injury, the brain must also constantly monitor the body’s energetic state via interoceptive signaling. This is accomplished by what we term *metaboception*: the *brain’s bidirectional monitoring and control of energy supply, demand, and transformation capacity*. Metaboception involves a neuroanatomically distributed set of key brain areas and circuitry, especially the brainstem, hypothalamus, and hippocampus<sup>1,8,9</sup>, as well as peripheral afferent peptidergic and metabolite signals from canonical “metabolic organs” that either supply energy (stomach, intestines)<sup>10</sup>, store energy (adipose, liver)<sup>11,12</sup>, transform energy (liver)<sup>13</sup>, and exhibit large fluctuations in energy consumption (skeletal muscles, immune system)<sup>5,14–16</sup> which have been extensively reviewed elsewhere (**Box 1**).

The less well-defined arm of metaboception relates to mechanisms that inform the brain of mismatch between energy *demand* and energy *transformation capacity*. If the rates of energy demand and the transformation capacity are properly matched, the organism can sustainably and efficiently fuel its operations through mitochondrial oxidative phosphorylation (OxPhos, converting food and oxygen into ATP). But if a mismatch arises between energy expenditure (e.g., excessive demand, arising from sickness or exhaustive exercise for example) relative to energy transformation capacity (e.g., limited mitochondrial OxPhos capacity), this creates an *energy gap*.

Energy gaps are direct threats to survival because organisms have access only to a finite energy budget and are thus energetically constrained<sup>17–21</sup>. So how are energy gaps sensed? Is the energy gap computed from multiple signals in the brain or locally in peripheral cells? The first third of this article covers the biology of GDF15, the second third discusses psychobiological processes underlying its regulation and link with the mind, and the last third covers downstream effects of GDF15 signaling and its health implications.

## Origin of energy gaps in mitochondria

To avoid persistent energy gaps, which may culminate in the deadly possibility of running out of energy, animals evolved multiple redundant pathways to sense energy gaps. Energy gaps can arise from two main sources<sup>14</sup>. One source is excess *energy demand*, which increases when normal yet costly cellular processes are activated, such as immune cell

activation, contraction, protein synthesis, and from so called “stress responses” that cost energy and therefore drive *hypermetabolism*<sup>22,23</sup>. A second source is impaired *energy transformation capacity*, which can result from inherited or acquired deficits in *mitochondrial OxPhos capacity*, or hypoxia, which restrict electron flow through the mitochondrial electron transport chain, ultimately reducing maximal ATP synthesis capacity<sup>24</sup>. Excess energy demand and reduced OxPhos capacity can also combine, as is the case in mitochondrial diseases<sup>25</sup> and aging/frailty<sup>26,27</sup>, further widening the gap between the rate of demand and what can be sustainably met.

As a form of distributed peripheral computation, the energy gap is then detected directly in each mitochondrion, or rather, in the distributed *Mitochondrial Information Processing System (MIPS)* together with other organelles including the nucleus<sup>28</sup>. Several mechanisms allow mitochondria to signal their functional states to the nucleus via “retrograde” signalling<sup>28-31</sup>, and then systemically via secreted proteins, metabolites, cell-free DNA, and possibly whole mitochondria<sup>28,31-33</sup>. Many of these signals are understood to represent general signals of impaired mitochondrial biology. However, they may in fact represent specialized metaboceptive signals informing the brain of the energetic state of its mitochondria. We term the processing of this signal *mitoception*: the brain’s *monitoring of the balance between cellular energy demand and mitochondrial energy transformation capacity*. An active challenge for the field lies in identifying the trigger(s) and purpose(s) for specific mitochondria-derived signals conveying information from organelle-to-brain.

Recent evidence in molecular and cell biology, as well as in clinical and epidemiology suggests a key mitoceptive signal: the cytokine/metabokine Growth Differentiation Factor 15 (GDF15)<sup>34,35</sup>. Across fields, GDF15 was independently discovered as a biomarker of aging that increases exponentially with age<sup>36-38</sup>, the top protein biomarker for dozens of current and future diseases<sup>39,40</sup>, the cause of morning sickness during pregnancy<sup>41</sup>, and a driver of cancer-related cachexia<sup>42</sup>. Physiologically, GDF15 is also elevated acutely during strenuous exercise (e.g., marathon running)<sup>43</sup>, but baseline circulating GDF15 is lower in regular exercisers who have higher mitochondrial OxPhos capacity conferred by increased mitochondrial biogenesis<sup>44</sup>. Clinically, GDF15 is also the top protein biomarker of primary mitochondrial diseases<sup>45-47</sup>, where genetic mitochondrial defects directly widen the cellular energy gap.

Our proposal is that GDF15 is a mitoceptive signal reflecting energy gaps. This body-to-brain signaling pathway resolves GDF15’s status as pan-disease marker, and reveals how psychobiological risk and resilience factors may converge, and in fact be integrated through energy, to shape human experiences and health trajectories.

### **Cellular metaboceptors and the body-to-brain axis**

Cells operate as computing agents<sup>48-50</sup>, constantly integrating their internal state and external signals to guide their behaviors and tune their physiology. A first cue into the purpose of the GDF15-based body-to-brain mitoceptive axis of communication is supported by the cross-tissue distribution pattern of GDF15 and its receptor.

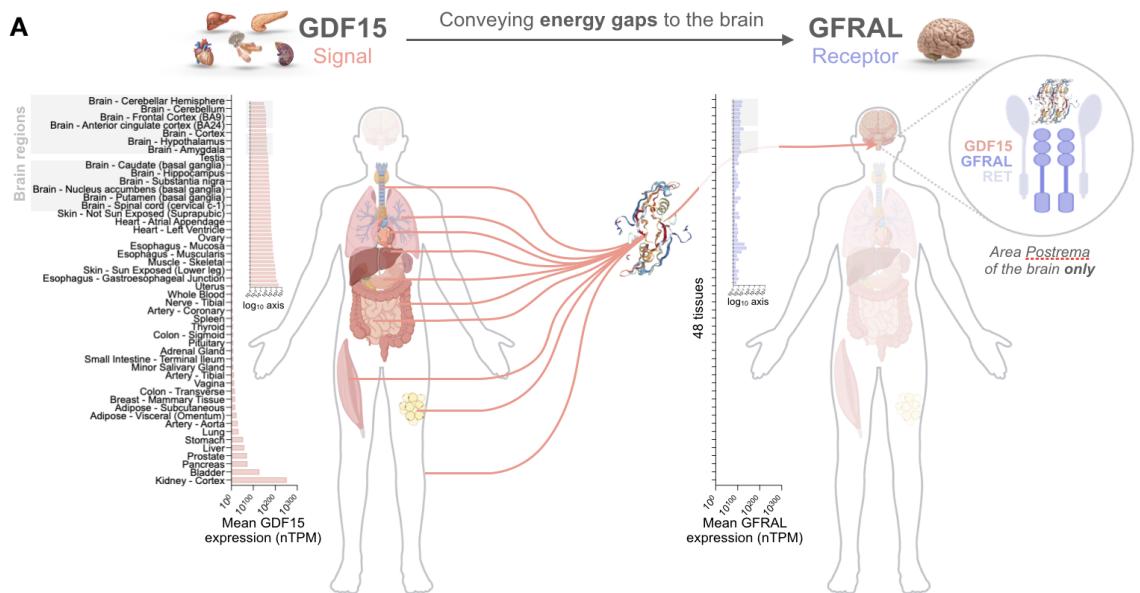
The gene *GDF15* is expressed across nearly all organs and tissues of the human body, although expression levels are particularly low in the brain. In bulk RNA sequencing data from 948 individuals, baseline brain GDF15 expression is ~300-fold lower than in the kidneys

(highest) (**Figure 1A**). However, it is possible that acute injury may induce GDF15 in the brain<sup>51</sup>.

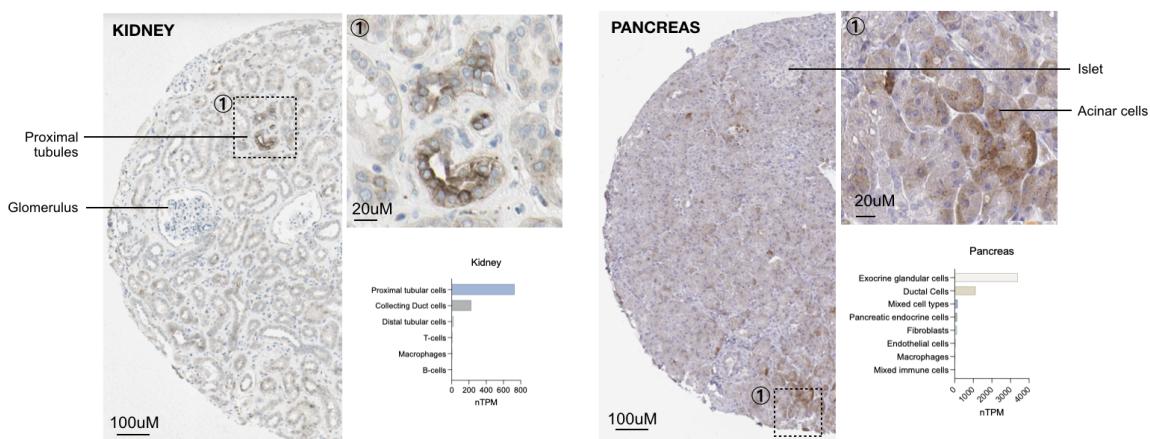
On the other hand, the only well-defined GDF15 receptor to date, GDNF family receptor α-like (GFRAL), is expressed in only one anatomically restricted region of the medullary brainstem including the area postrema and immediately adjoining medial nucleus of the solitary tract (NTS)<sup>52</sup>, both of which contains GFRAL-positive neurons<sup>53-57</sup> (**Figure 1A**). While the NTS receives ascending interoceptive signals directly from the nodose ganglia of the vagus nerve, the area postrema acts as a “circumventricular organ” by virtue of being highly vascularized by fenestrated capillaries. Pores between the vasculature and the area postrema allow relatively free passage of large macromolecules (e.g., proteins and peptide hormones) into the brain that would otherwise remain segregated from the brain via the blood brain barrier<sup>58,59</sup>. This mutually exclusive body-brain distribution pattern for the GDF15-GFRAL signal-to-receptor system provides a remarkable example of a body-to-brain afferent axis of metaboception.

Just as the brain computes a global, systemic summary of the organism's current and future energetic state in the context of metaboception construed broadly, we propose that cells and their MIPS locally compute their current and anticipated (likely short-term) energetic state in the context of mitoception. Each cell-mitochondria unit then emerges as a *metaboceptor*: an energetic sensor unit that locally computes the energy gap and relays that information to the brain. As reviewed below, the major signaling cytokine used to signal a cell's energy gap to the rest of the organism is GDF15<sup>60</sup>.

The expression pattern for GDF15 reveals that among high expressing organs, only specific cell types exhibit high GDF15 RNA and protein levels (**Figure 1B**, additional organs in **Supplemental Figure S1**)<sup>61</sup>. For example, in the kidneys, only the proximal tubule cells express GDF15, whereas cells of the glomerulus are negative for the GDF15 protein. Similarly, in the pancreas, GDF15 was only expressed in the acinar cells, and not in islet cells. Thus, specialized cell types in various organs, largely but not exclusively secretory cell types, appear to act as dedicated metaboceptors capable of alerting the brain of the energy gap at a specific point in time. This cell specificity calls for more spatially and temporally resolved studies to examine local cellular metaboception and mitoception mechanisms that initiate the afferent arm of organismal mitoception.



**B** Tissue heterogeneity and cell-specific GDF15 distribution for cell-level metaboception



**Figure 1. The GDF15-GFRAL body-brain axis.** (A) The *GDF15* gene is expressed in all human tissues, except the brain<sup>61</sup> (left, tissues ranked by *GDF15* expression level). Some brain regions show trace *GDF15* expression but represent <1% of the median of other somatic tissues. In contrast, although *GFRAL* may be expressed at some levels in some non-brain mouse tissues, *GFRAL* is expressed *only in the human brain*, and not in any appreciable levels in any of the dozens of other somatic tissues examined<sup>53</sup> (right). In the GTEx dataset<sup>62</sup>, *GFRAL* exhibits trace expression (mRNA levels < 1 normalized transcript per million, nTPM) in adipose tissue, testes, and breast tissue, but the protein is not detected in these tissues (right, tissues in same order as for *GDF15* expression panel). Note that the medullary brainstem including the area postrema and nucleus of the solitary tract (NTS), which contain *GFRAL*<sup>+</sup> neurons, are absent from this dataset. Thus, this polarized distribution illustrates a body-to-brain mitoception signaling axis where *GDF15* made by peripheral metaboceptors directly signals onto the brain, as previously discussed<sup>34</sup>. (B) Immunolabeling of *GDF15* in human tissue sections from selected organs showing cell-type specific expression and regional heterogeneity in *GDF15* protein abundance in the kidney and pancreas. Images from other organs are available in *Supplemental Figure 1*. The inset shows *GDF15* RNA transcript levels from single cell RNA sequencing in each tissue from the Human Protein Atlas<sup>63</sup>. *GDF15* expression is averaged by major cell types.

## **Part 1 – AFFERENT ARM OF MITOCEPTION**

In the following sections, we review the *afferent arm* of GDF15-based mitoception. We begin with the molecular and cellular processes that frame cells as metaboceptors capable of releasing GDF15 into the circulation. Next, we review the concept of reductive stress<sup>64</sup> as the trigger for the integrated stress response (ISR), the gene program that triggers GDF15. We show how GDF15 is also a primary biomarker of mitochondrial defects as well as other chronic illnesses, which together point to energy gaps as the common features of many disease states. We close this section by discussing how GDF15 is acutely inducible by mental stress, and how it is generally elevated in response to chronic psychosocial stressors, adversity and psychiatric disorders, pointing to the psychobiological convergence of psychosocial and biological stressors through mechanisms linked to energy regulation.

### **The molecular origin and triggers of GDF15 converge on reductive stress**

Cells communicate with each other in part through cytokines, a family of small, secreted proteins. Some cytokines are produced by very specific cells to convey specific signals (e.g., between immune cells during an immune response), while other cytokines are expressed non-specifically by several organs in response to stress<sup>60</sup>, including the widely studied interleukin 6 (IL-6)<sup>65</sup>. GDF15 is another small cytokine, often referred to as a metabokine (or mitokine) based upon its induction by metabolic stressors and mitochondrial disorders<sup>66,67</sup>.

Several chemical and intracellular processes can trigger GDF15<sup>68,69</sup>, but a point of convergence for across stressors appears to be *reductive stress*<sup>45,70,71</sup>. Reductive stress sits at a biochemical hub and reflects the state of cellular electron flow<sup>64</sup>. In breathing creatures like humans, energy flux converges in mitochondria, where oxidative phosphorylation (OxPhos) transforms food-derived electron flow into an electrochemical gradient used to synthesize ATP<sup>7</sup>. But when oxidative capacity is limited or insufficient relative to the cellular energy demand, electrons face excess resistance and cannot as easily flow through the OxPhos system<sup>72</sup>. This causes *energy transformation deficiency* and electron “backflow”<sup>70,73</sup>. The biochemical consequence of this backflow is the accumulation of electrons on the electron acceptor NAD<sup>+</sup>, transforming it to its reduced form NADH.

The increase in NADH:NAD<sup>+</sup> ratio is a primary measure of reductive stress<sup>70</sup>. It also drives cellular reprogramming across various contexts<sup>64,74</sup>, and experiments manipulating the NADH:NAD<sup>+</sup> ratio directly show that reductive stress alone is sufficient to trigger GDF15 secretion<sup>70,71</sup>.

When the energy transformation capacity of a cell or tissue is exceeded by the cell’s energy demand, reductive stress activates a highly conserved genetic program called the integrated stress response (ISR) through several potential mechanisms<sup>75</sup>. Within the mitochondria, a high NADH:NAD<sup>+</sup> ratio can limit TCA cycle function, causing amino acid starvation, thereby activation the ISR kinase GCN2 and downstream transcription factors including ATF4 and CHOP<sup>70</sup> which in turn induces *GDF15* expression<sup>76</sup>. Additionally, mitochondrial dysfunction associated with elevated NADH levels can activate ISR via the

OMA1-DELE1-HRI pathway<sup>77</sup>. In this pathway, mitochondrial stress caused by disrupted ATP production activates the protease OMA1, which cleaves DELE1, releasing fragments that activate cytosolic HRI kinase and initiate the ISR through phosphorylation of eIF2α.

Alternatively, reductive stress could indirectly induce ER stress through impaired ATP-dependent protein folding and disturbed ER redox balance. This stress would trigger the ISR through activating the ER kinase PERK. The intracellular energy sensor AMP-activated protein kinase (AMPK) may also, at least in some certain cell types, trigger ISR activation and GDF15 production<sup>78</sup>. Despite these proposed mechanisms, direct empirical evidence remains necessary to determine which ISR kinase most widely drives GDF15 production under physiological reductive stress conditions.

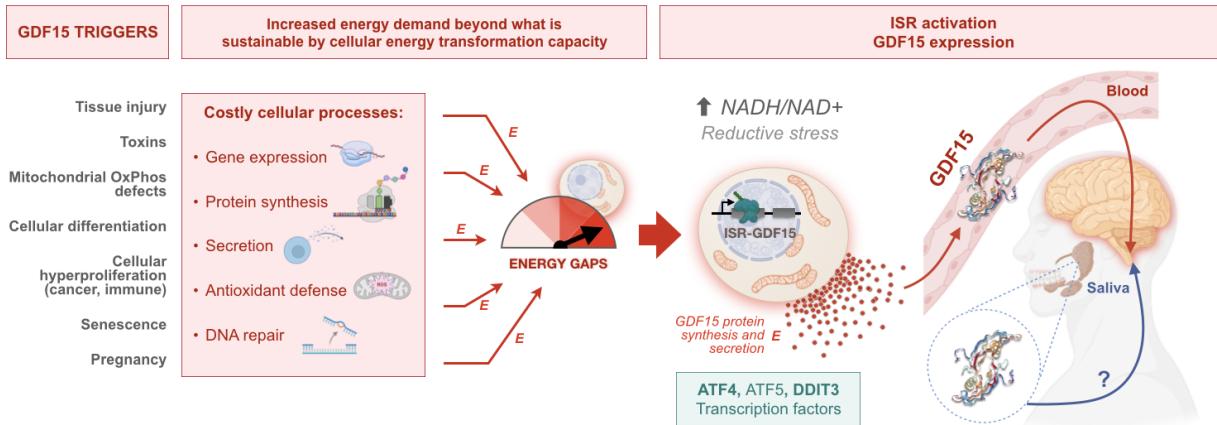
Once the ISR induces *GDF15* gene expression, the resulting protein is synthesized and secreted as a GDF15 homodimer cytokine into the bloodstream (other variants may exist, see<sup>69</sup>). Carrying the signal of an energy gap from a cellular metaboceptor, GDF15 travels to the brain to close the “afferent” arm of mitoception.

### Mitochondrial defects are a direct trigger of GDF15

This *mitochondria*→ISR→GDF15 cascade has gained attention across fields of basic and clinical research. GDF15 is the leading circulating biomarker of mitochondrial OxPhos defects that cause rare mitochondrial diseases<sup>45-47</sup>. Compared to regular levels of GDF15, which are around 100-500 pg/ml in healthy middle-aged individuals with normal oxidative capacity, individuals with OxPhos defects can have chronically elevated GDF15 levels around >1000-5000 pg/ml.

Another product of the ISR, fibroblast growth factor 21 (FGF21) is elevated in MitoD and signals onto the brain<sup>46,79</sup>. FGF21 is upregulated by at least some arms of the ISR, but in comparison with GDF15, it is a more pleiotropic hormone regulated more strongly by fasting and feeding in ways that GDF15 is not<sup>80</sup>. Thus, FGF21 and other molecules play important signaling roles in metaboception, but do not appear as specific mitoceptive signals in the same way as GDF15.

Experimentally, the *mitochondria*→ISR→GDF15 secretion signaling axis has been confirmed in cells where OxPhos defects are genetically or pharmacologically induced. Acutely interfering with electron flow in the OxPhos system upregulates GDF15 by several-fold, together with related transcription factors (e.g., ATF4/5) and coregulators (e.g., CHOP)<sup>70,81,82</sup>. In one study where OxPhos was chronically inhibited with Oligomycin (inhibitor of the ATP synthase, 1nM), GDF15 expression was increased >32-fold after 1-2 weeks<sup>24</sup>. In vivo, selectively perturbing mitochondria by deletion of nuclear genes encoding OxPhos subunits or mtDNA-related proteins in mice triggers ISR induction and GDF15 production<sup>83</sup>, and the same response is observed in humans with mtDNA mutations<sup>45,61</sup>. Thus, GDF15 is a robust marker of mitochondrial OxPhos defects that cause energy gaps (**Figure 2**).



**Figure 2. Triggers of GDF15 secretion converge on energy deficiency, reductive stress, and ISR activation.** Stressors trigger the activation of molecular, organelar and cellular behaviors that cost energy. In many well documented cases, physical, chemical, and mental stressors produce reductive stress reflected in the increase in the NADH/NAD<sup>+</sup> ratio and lactate production. Reductive stress is a potent trigger of the integrated stress response (ISR), a gene program that inhibits certain costly cellular operations, and signals to other cells the presence of energetic stress via extracellular GDF15 secretion. GDF15 is secreted in various biofluids (blood, cerebrospinal fluid, saliva, urine, others). In the blood, GDF15 eventually reaches its cognate receptor in the area postrema of the brain to mobilize a dual energy conservation and mobilization response. Although the GDF15 protein is found and inducible in human saliva<sup>50</sup> whether and how saliva GDF15 signals to the brainstem remains unknown.

### GDF15 as a general marker of disease states

In addition to OxPhos defects, *GDF15* expression and release into circulation is induced by several other energy-costly physiological states, although the underlying molecular pathways are, in many cases, not yet clear. For example, circulating blood GDF15 is elevated ~200-fold in pregnancy<sup>84</sup>. It also increases exponentially ~100-150% on average per decade of life with aging<sup>37,85,86</sup>, making it a robust aging biomarker. There are also natural diurnal variations in mouse plasma GDF15 mRNA and muscle protein<sup>87,88</sup>, and in human blood and saliva GDF15 protein<sup>89,90</sup>.

In relation to disease, unbiased proteomic surveys searching for pan-disease markers have identified GDF15 as the most consistently elevated protein linked to any illness. Individuals with diagnoses of common chronic illnesses including cardiovascular disease<sup>91</sup>, kidney disease<sup>92</sup>, cancer<sup>93</sup>, Alzheimer's disease<sup>94,95</sup> autoimmune diseases<sup>96</sup> exhibit elevated circulating GDF15 concentration. Across dozens of medical diagnoses, GDF15 was the most consistently and significantly elevated circulating cytokine, over and above immune and non-immune cytokines like interleukins, growth factors, and others tissue-specific proteins<sup>39,40</sup>.

Moreover, across two prospective studies, GDF15 predicted 10-20-year disease onset, including cognitive dysfunction and dementia<sup>39</sup>, better than most other brain and non-brain proteins<sup>39</sup>. Together, these findings demonstrate robust associations linking circulating GDF15 to costly metabolic conditions including human diseases and a spectrum of disease-related traits and symptoms. *Why does GDF15 mark such a broad range of pathological states?*

Nothing in biology is “free”<sup>22,23,97</sup> – every process costs energy and must be “funded” from a limited budget<sup>16,72,73</sup>. As a result, energy is the most vital currency and consilience point in both health and disease. Taken from first principles, responding to sickness and the energetic cost of growth, maintenance, and repair (GMR) processes<sup>23</sup> creates an energy sink. Like a tumor stealing energy away from surrounding tissues, disease- and stress-related energy sinks force trade-offs that redirect energy away from health-promoting processes, leaving other parts of the organism more vulnerable to the onset of further disease.

We propose that the reason why GDF15 is both elevated across dozens of diseases and disorders, and why it also is predictive of future incident disease<sup>39,40</sup>, is because *GDF15 signals ongoing competition for energy within the constrained organismal energy budget*<sup>22,26,97</sup>. If one cell or organ experiences an energy gap, it saps energy from a competing system, curtailing its normal function(s) and ability to heal through GMR processes.

Interestingly, GDF15 is also elevated in conditions considered to exhibit and energy surplus, such as in diabetes and obesity<sup>39</sup>, where circulating GDF15 levels scale with increase adiposity<sup>69</sup>. The reason why metabolic surplus—or ‘oversupply’ relative to cellular energy demand—trigger GDF15 likely is because excess energetic substrates elevate NADH, thereby driving reductive stress<sup>98,99</sup>. Thus, both excess electron influx or insufficient oxidation by mitochondria can drive reductive stress and GDF15 signaling, potentially indicative of the relative inability to transform energy relative efficiently<sup>98</sup>.

Finally, this energetic perspective on health also positions stressors, such as chemotherapy<sup>100</sup>, or even responding to drugs that act by inhibiting mitochondrial OxPhos such as metformin<sup>101</sup>, as converging on the same energy gap, which culminates in GDF15 signaling.

### ***Psychosocial stress elevates circulating GDF15***

#### *Cellular and experimental clinical studies*

Both disease states and stress responses induce energetically costly processes and allostatic adaptations<sup>23</sup> (see **Figure 2**). As a result, hormones secreted during stress<sup>22</sup> and mitochondrial OxPhos defects<sup>24</sup> both increase overall energy expenditure (i.e., *hypermetabolism*). The common hypermetabolic effects of disease states and stress are likely driven by compensatory increases in cellular and physiological activities: gene expression, protein synthesis and secretion, physiological changes including increased heart rate and neural activity, and behavioral features including hormonal responses and increased muscle tone – all hallmarks of stress responses<sup>25,102</sup>. It costs energy to “activate” anything. The stress response is, therefore, fundamentally an energetic response. And canonical “stress” systems<sup>103</sup> studied for nearly a century are deeply intertwined with metaboception.

If cells act as metaboceptors in which the ISR→GDF15 axis is non-specifically activated by an energy gap, then any threat or challenge that directly or indirectly increases energy demands (or is predicted to increase demands) should stimulate mitoception via the ISR→GDF15→GFRAL axis. In social animals, threats include *perceived* threats to one’s physical and psychological identity (i.e., the self) or to one’s social group. On the other hand, sociality and affiliation afford energy savings and are linked to longevity<sup>104</sup>.

Likely for this reason, social isolation or exclusion may represent energetically costly stressors that trigger the ISR→GDF15 axis, simultaneously activating energy-mobilizing “stress” axes such as the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), which increase energy expenditure <sup>23,105</sup>. Indeed, three independent studies show that socio-evaluative stress increases both blood and saliva GDF15 <sup>106,107</sup>. After the onset of 5-10-min laboratory speech tasks, GDF15 increased on average by ~3-6% after 5-10 minutes in blood, and by ~28-43% within ~10-20 minutes in saliva <sup>90</sup>. In both biofluids, GDF15 elevations occurred within minutes and were followed by rapid recovery (within 5-10 minutes) <sup>90</sup>, a pattern consistent with pulsatile release of other metabolic and so called “stress” hormones. In mice, acute restraint stress similarly increased blood GDF15 <sup>108</sup>. These experimental studies demonstrate that the rapid control of GDF15 secretion extends beyond cell-autonomous mechanisms and may also be driven by (systemic) reductive stress. Lactate, a metabolite whose concentration reflects tissue reductive stress (NADH/NAD<sup>+</sup>), also transiently increases with mental stress alone both in humans <sup>90</sup> and mice <sup>109</sup>. Thus, the energetically costly state of mental stress appears sufficient to rapidly trigger reductive stress and elevate circulating GDF15 in human biofluids.

#### *Epidemiological studies*

The role of *GDF15* in psychosocial stress is further supported by initial clinical and cohort studies linking psychopathology and adverse social circumstances to GDF15 levels. In studies of mental illness, relative to controls, individuals with psychiatric diagnoses of major depressive disorder, bipolar disorder and psychosis had 40-78% higher blood GDF15 levels <sup>110-114</sup>, with effect sizes of 0.35–5.2 (average 1.95, median 1.12, n=4 studies). This compares with other cytokines, including IL-6, IL-1b, TNFa, CRP, which have effect sizes ranging from -0.05–9.01 (average 1.41, median 0.41, n=45 studies) in depressive and bipolar disorders <sup>115-117</sup>. Poverty, low household income, and low education levels associated with unfavorable social position were also linked to higher blood GDF15 <sup>118,119</sup>.

In relation to social stressors, data from >52,000 UK Biobank individuals in a proteome-wide study of 2,920 plasma proteins, GDF15 was the top protein associated with perceived social isolation and loneliness <sup>120</sup>. Individuals struggling with community engagement or scoring high on neuroticism also exhibit elevated blood GDF15 levels <sup>120</sup>. These data support the existence of a link between psychosocial factors, energy, and metaboception. It is, however, important to consider that there are many other non-psychosocial factors in poverty that could contribute to increased energy demands and to mitoception.

Importantly, participation in social activities involving energetically costly physical activity was negatively associated with GDF15 <sup>39</sup>. This could potentially reflect the protective “energy-saving” effects of a social support system (minimizing threat to the self), the benefit of physical activity in enhancing mitochondrial energy transformation capacity <sup>121</sup>, or other factors that prevent cellular energy gaps by either increasing capacity or reducing costs. Finally, individuals with comorbid mood disorders and physical illnesses (stroke and sex hormone imbalance) also exhibit higher blood GDF15 <sup>122-125</sup>, possibly reflecting a compounded effect of biological and psychological challenges on circulating GDF15.

Altogether, these human data suggest that at least some cellular metaboceptors signal to the brain not only in response to physically injurious stimuli but also in response to perceived *mental* threats, acting to regulate the energetic state of the body. As reflected in post-stress blood lactate increases<sup>106,109</sup>, mental stress appears to induce reductive stress (elevated NADH/NAD<sup>+</sup> ratio) within minutes via mechanisms that remain unknown. In line with such a *threat-GDF15* connection, GDF15-deficiency in mice reduced the propensity to avoid open spaces (anxiety-related behaviors)<sup>126</sup>, while chronic GDF15 overexpression (ectopic skeletal muscle uncoupling protein 1 expression) led to more anxiety-related behaviors<sup>88</sup>.

These findings suggest that states of mind are related to circulating GDF15 levels, both of which involve the brain, and raise the question of what it "feels" like to have elevated GDF15 concentrations in the blood—an issue explored in the next section.

## Part 2 – EFFERENT ARM OF METABOCEPTION

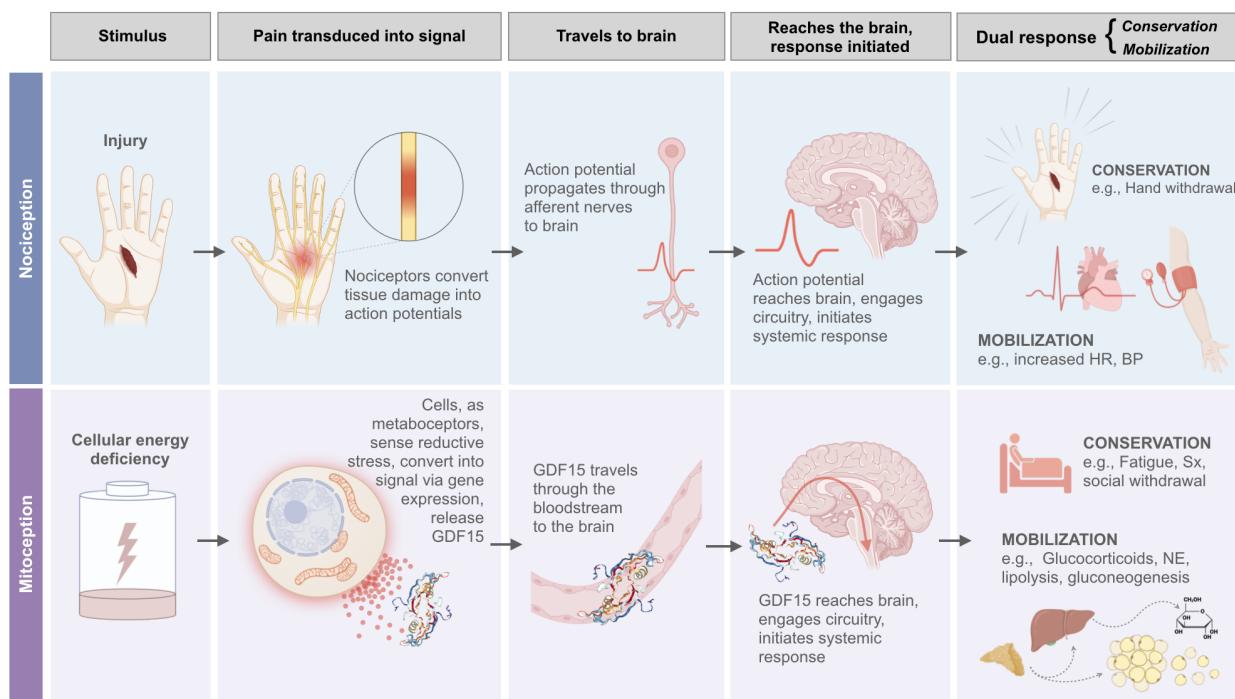
Having discussed cellular, physiological, and psychosocial drivers of energy gaps and how they are translated into GDF15 within cells, in this section we discuss what happens when the brain senses the presence of GDF15. *What kinds of responses and anticipatory states does the brain produce when it senses energy sinks?*

We propose that the *efferent arm* of metaboception involves a dual response that simultaneously mobilizes energy resources to ensure plentiful supply to energetically deficient cells, while conserving energy at the whole-body level to by redirecting energy to areas of highest priority, balancing out the limited organismal energy budget. Finally, we discuss fatigue as the resulting integrated experience of mitoception, positioning fatigue as a transdiagnostic experience of energy gaps.

### Dual brain response to GDF15

Within cells, the energy-sensing ISR operates in a two-pronged manner. It transcriptionally suppresses energy consuming processes including protein synthesis<sup>127</sup> to address energetic *demand* challenges, while simultaneously activating processes that recruit energetic resources<sup>128</sup> and address energetic *supply* challenges. Similarly, cellular and organismal energy sensing systems aim to promote survival via a dual response that simultaneously conserves and mobilizes energy<sup>14</sup>.

A useful analogy to metaboception and mitoception is nociception, where a stimulus is transformed into an experience. Nociception processes a painful stimulus and elicits the appropriate dual response to ensure the organism's safety (**Figure 3, top**). In this context, we can conceive of a cellular energy gap as kind of "energetic pain". Below we describe how the brain responds to mitoceptive stimuli in two main ways: **1)** by mobilizing energy from existing reserves, and **2)** by conserving energy normally directed to energetically costly, but not acutely essential, processes (**Figure 3, bottom**).



**Figure 3. Mitoception via GDF15 mirrors nociception.** A skin wound is transduced into pain by nociceptors, transmitted to the brain via small caliber, unmyelinated nerve fibers where they activate specialized brain areas involved in nociception. These brain areas project onto complex brain circuitry that unleash a dual, pro-survival conservation or preservation strategy, and an arousal response that mobilizes energy resources to face the potential injury or threat. Mitoception operates following a parallel system. The cellular energy gap is transduced into energetic pain by the reductive stress/ISR system, transmitted to the brain via the blood-secreted protein GDF15 that activates GFRAL-positive neurons in the area postrema, involved in sensing circulating toxins and other noxious substances. The area postrema projects onto complex brain circuitry to unleash a dual response involving multi-system *energy conservation* (i.e., fatigue, sickness behavior (Sx), social withdrawal) and *energy mobilization* (i.e., glucocorticoids, catecholamines cooperating to increase glucose and fatty acid concentrations in the blood).

### 1. Energy mobilization

Energy mobilization involves recruiting and diverting existing energetic resources from one part of the organism towards the systemic circulation, or towards the cells/tissue in need. One example is during exercise where blood is shunted away from digestive organs, towards active muscles. Endocrine examples of energy mobilization include the release of glucose into the blood by the liver in response to stress mediators such as glucocorticoids, catecholamines and cytokines<sup>129</sup>, and of fatty acids from adipose tissue<sup>130</sup>. These “stress response” axes are in fact energy mobilization axes, co-opted during evolution by the brain/mind system to mobilize energetic resources to feed stress responses<sup>131</sup>. GDF15, together with GFRAL, has also been shown to be involved in such responses.

Studies in mice have demonstrated that activation of the *GDF15*→*GFRAL* axis in the brain activates the HPA and SNS axes and contributes to anxiety. This induces corticosterone

and adrenaline release<sup>53,100,132</sup> which can trigger the breakdown of energy stores through lipolysis and gluconeogenesis to maintain blood sugar<sup>53</sup>, thereby providing energetic resource delivery to meet the acute energy requirements of the energetically aching cells/tissue of origin<sup>128</sup>. Although GDF15 itself has not yet been directly shown to increase glycogen breakdown or gluconeogenesis, GFRAL+ signaling stimulates lipid oxidation<sup>53</sup>. Effects of GDF15 on lipolysis in adipose tissue<sup>133</sup> and on glucose regulation and insulin sensitivity<sup>69,134</sup> also contribute to the notion that GDF15 plays a role in redistributing energy across the organism.

In humans, individuals who are energetically challenged, such as patients with mitochondrial disease and primary OxPhos defects, exhibit an endocrine signature of SNS hyperactivation and energy mobilization<sup>45,135-137</sup>. As mentioned above, excessive SNS activation occurs alongside elevated circulating GDF15, although it remains unclear whether basal levels of circulating GDF15 contributes to SNS hyperactivation in humans (or vice versa, or unrelated).

Robust evidence also shows that circulating GDF15 signaling contributes to anxiety-like behavior in mice<sup>108</sup>, and that the anxiogenic effects of injected adrenaline depend on the GDF15→GFRAL body-to-brain signaling axis<sup>108</sup>. GDF15 was also the most strongly upregulated protein associated with anxiety in the UK Biobank<sup>39</sup>. Furthermore, both SNS activity and GDF15 are elevated as we age<sup>85,86</sup>, possibly reflecting the energetic mobilization required to fuel the costly stress responses (repair of accumulated damage and compensation) during aging<sup>138</sup>.

The recently uncovered role of GDF15 in triggering the classic autonomic nervous system and neuroendocrine stress responses provides a new perspective on past studies of acute and chronic stress. In past studies of human participants experiencing psychosocial stress, physiological stress and cortisol, SNS-derived hormones including catecholamines in blood or urine, and metabolic/cardiovascular markers such as elevated blood glucose and lipids were previously understood to be part of the most rapid and proximal stress responses. But given that mental stress induces GDF15 that interact with other neuroendocrine factors within minutes<sup>90</sup>, it is possible that GDF15 could act simultaneously and interactively with classical “stress response” axes.

## 2. Energy conservation

Energy conservation involves sparing portions of the organism’s limited energy budget by suppressing behaviors and functions not essential to survival<sup>26,97</sup>. Acutely de-prioritized systems may include cellular growth, maintenance and repair (GMR) processes, as well as digestion, higher order cognitive processes, maintaining body temperature, and sustaining the intensity or amount of physical activity<sup>139</sup>. The NADH:NAD+ ratio reflects the resistance to electron flow (energy resistance, éR)<sup>72</sup>, which we refer to here as the energy gap. In flies, this directly shapes behaviors, driving the pressure to sleep<sup>140</sup>. Similarly in humans and other animals, GDF15 signaling of an energy gap could underlie behavioral changes that aim to conserve energy, including but not limited to fatigue.

Perhaps one (counterintuitive) way to rapidly save energy is to fast. While there is a net long-term energetic resource gain to forage, find and eat food, in the short-term anorexia conserves energy because digestion—like everything else in biology—costs energy: 5-10% of

total daily energy expenditure is used to digest<sup>141</sup>. Not eating may spare this portion of the energy budget. At physiological levels, GDF15 is a known anorectic and nausea-inducing signal, reducing the motivation to eat<sup>41,142,143</sup>. As proposed previously<sup>34</sup>, nausea and vomiting might also prevent the ingestion of toxins. In line with that idea, morning sickness or hyperemesis gravidarum during the early stages of pregnancy caused by elevated GDF15<sup>41</sup> have been proposed as a mechanism to guard the organism against potentially costly and harmful exposures. However, more work investigating the potential immediate energetic consequences of GDF15-induced anorexia, nausea and emesis is required to fully understand its role in mitoception in general, and whether this contributes to energy conservation.

The *GDF15→GFRA1* axis also conserves energy. In mice, GDF15 signaling decreases body temperature and achieves an energy-saving torpor-like state<sup>53</sup>. In humans, among individuals with primary mitochondrial OxPhos defects, as in many chronic illnesses<sup>144,145</sup>, the most common symptom is fatigue: the subjective experience of lacking energy and the capacity for doing things, likely reflecting the need to conserve energy to close the energy gap. Among patients with mitochondrial diseases, physical and mental fatigue are associated ( $r=0.27-0.53$ ) with circulating GDF15<sup>61</sup>. Together with preclinical work linking GDF15 signaling to torpor<sup>53</sup>, these findings suggest that GDF15 may promote energy conservation by inducing fatigue (**Box 2**).

### ***Does mitoception induce fatigue to conserve energy?***

The experience of fatigue alters behavior to promote survival by reducing energy expenditure<sup>5</sup>. People experience fatigue during or after energetic challenges including vigorous exercise and sickness. Decreased motivation to engage in physical, mental and social activities, and feeling weak and inclined to rest together with other negative valence emotions decrease unnecessary energy expenditure. This phenomenon, known as “sickness behavior,” is understood to (re)allocate energetic resources to prioritize urgent recovery and healing processes<sup>5</sup>, as in the context of aging and frailty<sup>26</sup> and recovery from injury and infection<sup>146</sup>.

### ***Psychological stressors contribute to fatigue***

The experience of fatigue is also associated with psychiatric disorders such as depression and anxiety, as well as negative psychosocial factors including psychological stress, and early life adversity. **Table 1** summarizes associations between psychiatric disorders and psychosocial exposures with the experience of fatigue. The body of evidence linking psychosocial stressors to fatigue appears magnified in the disease-related fatigue literature. Fatigue is greater in those reporting negative psychosocial factors, whereas those reporting more positive psychosocial factors experience less fatigue<sup>147-154</sup>. This apparent compounding effect of psychosocial and diseases-related stressors on fatigue could relate to the fact that both psychosocial stress (see above) and diseases independently increase circulating GDF15.

### ***Emotional well-being is related to lower fatigue***

In contrast, negative associations have been found between fatigue and positive psychosocial factors such as social support and optimism (see **Table 1**). This suggests that positive psychosocial factors could allow an individual to either mitigate or minimize the impact

of energetic challenges and deficits. The exact mechanisms for their potential buffering effects need to be explored further. This includes whether they are buffering the direct effects of stress or if they have direct effects themselves. Positive resources such as support and emotional well-being can impact physiology both through direct effects as well as moderators of stress effects<sup>105,155</sup>.

### *GDF15 as a nexus for psychosocial stress, fatigue, and metabolic disease?*

We propose the hypothesis that psychosocial and disease factors represent energetic challenges that act via GDF15 to produce fatigue. We experience fatigue when energy expenditure exceeds our system's actual or predicted ability to transform energy. As introduced by Dantzer<sup>5</sup>, our immune system can subjugate the brain into rest/recovery mode<sup>5</sup>, preserving energy resources to fuel the most vital processes<sup>26</sup>, including immune processes<sup>156</sup>. Beyond immune activation and injury, several psychosocial factors have been related to the experience of fatigue (**Table 1**). Could psychosocial and other lived experiences affect our perception of energy and fatigue via GDF15? If GDF15 induces fatigue, the mental stress→GDF15→fatigue axis could explain why psychosocial stressors, traumatic exposures, and mental illness promote fatigue (along with cytokine release). This axis would be adaptive via its ability to promote energy conservation, thus allowing redirection of energetic resources to face the primary stressor<sup>23</sup>. This notion is indirectly supported by evidence showing that GDF15 is elevated in several diseases and in aging<sup>40,85,86</sup>, states where individuals also report fatigue<sup>144</sup>. Work in elderly populations also demonstrate a positive association between GDF15 levels and frailty, including measures of exhaustion and weakness<sup>157,158</sup>.

Psychosocial factors including rest, social habits and conviviality that modify GDF15 levels<sup>159</sup> also contribute to fatigue and frailty<sup>160,161</sup>. Preliminary findings from the UK Biobank show that feelings of low energy, aversion to physical activities such as taking the stairs and walking for pleasure, an inability to participate physically and mentally in social activities, along with a number of negative psychological states are linked to elevated GDF15 (**Table 2**)<sup>39</sup>. The reasons for the associations between poverty/household income with GDF15 could be many, mediated by physical factors such as the environment, underlying biological or biochemical conditions, or medication. Nonetheless, facing such challenges is predicted from the energetic cost of stress responses<sup>23</sup> be energetically demanding. One interpretation is that individuals with elevated GDF15—indicative of chronic energetic deficiency—develop an aversion to mental, physical, and social factors that could further drain their energy reserves.

Further work, however, is needed to investigate the direct and indirect effects of stressors on fatigue and other (negative or positive) subjective experiences, and their potential mediation by circulating GDF15. **Box 2** highlights the type of studies needed, spanning different levels of spatial and temporal resolutions, to decipher how GDF15 interact with other factors to shape states of mind and human behaviors.

### *GDF15: context matters*

Complex human experiences are not defined by single factors. How an individual experiences GDF15 as a signal for energetic deficiency and fatigue may vary depending on the context under which it is experienced. For example, exercise acutely increases GDF15 (like

other cytokines) within minutes to hours, but lowers baseline circulating GDF15 in those who exercise regularly<sup>44</sup>. It is also possible that acute exercise induces elevated GDF15 through intermediate processes, such as ER stress<sup>162,163</sup>. Exercise induced mitochondrial biogenesis<sup>164</sup> and a related increase in the individual's energy transformation capacity<sup>121</sup> driven by elevated mitochondrial density could make daily challenges relatively less energetically "stressful," buffering against reductive stress, contributing to lower baseline GDF15 levels in trained individuals<sup>44</sup>. However, when GDF15 remains chronically elevated, the sustained suppression of appetite and exercise avoidance may become maladaptive. In cancer cachexia, where GDF15 is elevated, blocking its signaling with an antibody may help prevent muscle loss<sup>165</sup>. In animals, removing the area postrema entirely also helps prevent peripheral effects<sup>166</sup>. With aging, the loss of muscle mass and frailty in sarcopenia could be in part driven by GDF15-based mitoception, as an attempt of the brain to conserve energy<sup>138</sup>.

## Conclusion and Outlook

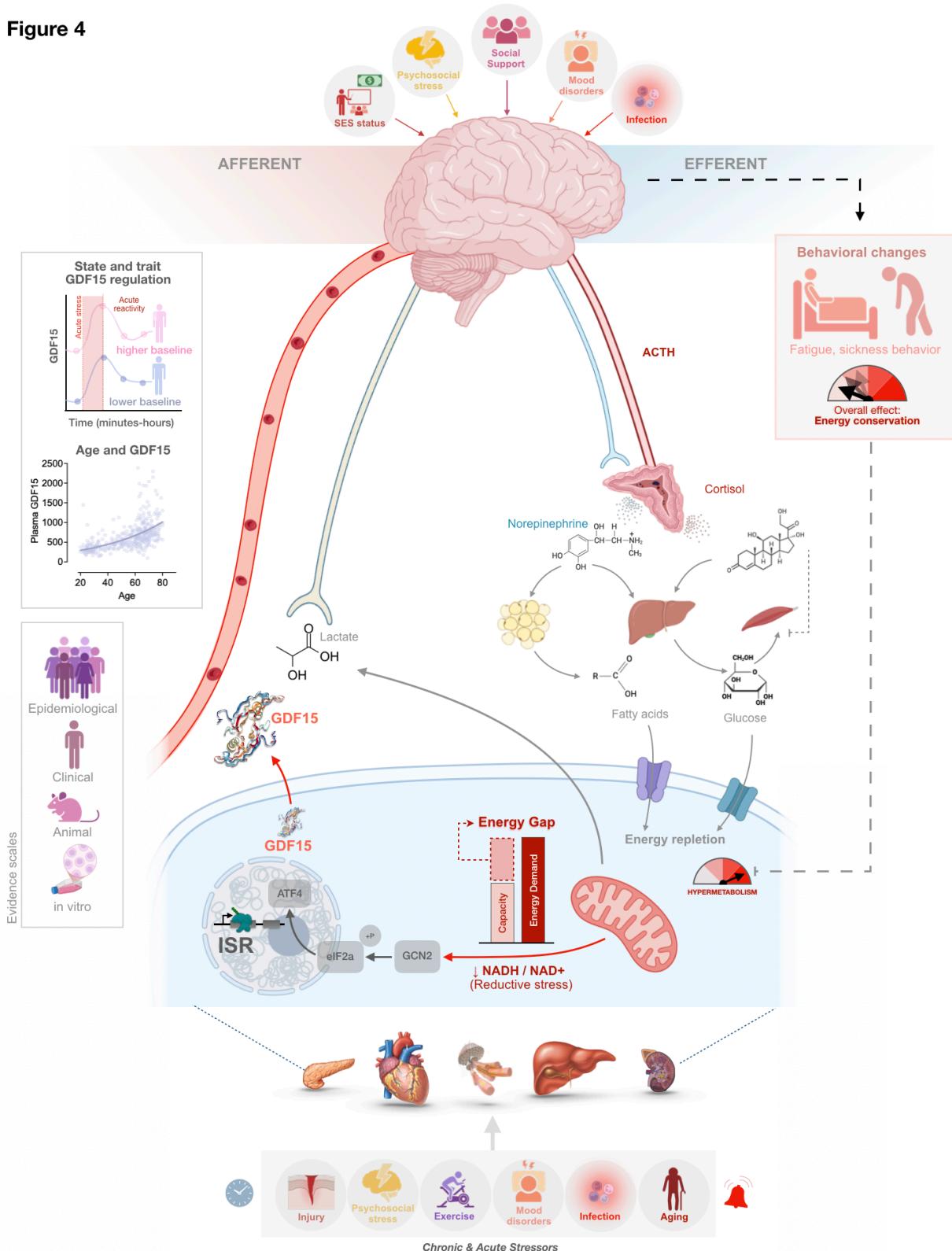
We propose that the mitoception arm of metaboception is conveyed in part by the *Energy gap→ISR→GDF15→Brain→Fatigue cascade* (**Figure 4**). Mitoception thus produces an integrated psychobiological state, which (although uncomfortable) likely promotes energy balance the face of energy-consuming events in the short term<sup>26</sup>. In the long term, this energy-conservation axis is predicted to promote health and survival<sup>138</sup>. Since mind and body converge and share the same energetic circuitry<sup>22</sup>, metaboception in general and mitoception in particular would naturally shape subjective experiences, physiology, behaviors and health outcomes.

An energetic perspective on health and disease operationalized by the mitoceptive body-to-brain GDF15 signaling axis leads to several *Outstanding Questions* ranging from mechanistic details of mitoception to neural pathways underlying the interaction between positive experiences of vigor, vitality, purpose in life, and well-being, and how they intersect with GDF15 levels and fatigue.

In summary, our model of mitoception suggests that GDF15 conveys the gap between energy demand and transformation capacity in mitochondria to the brain. The purpose of this signaling axis is to preserve optimal functioning, in part by shaping a felt sense of energy deficiency. An organism's energy budget is finite and must be efficiently managed<sup>26,97</sup>. By bidirectionally monitoring and regulating energy metabolism, mitoception in concert with other cellular and systemic metaboceptive pathways thus redirect the organism's limited energetic resources towards processes that promote allostasis and well-being.

The convergence of psychobiological processes onto energy and metaboception opens new exciting avenues to build a holistic understanding of the processes underlying human health across the lifespan.

**Figure 4**



**Figure 4. The mitoceptive subset of metaboception.** Afferent arm: cellular metaboceptors distributed across human tissues (bottom) sense the energy gap driven by excess energy demand or expenditure

relative to mitochondrial energy transformation capacity. This activates the integrated stress response (ISR) via reductive stress (elevated NADH/NAD<sup>+</sup> ratio), triggers extracellular GDF15 release, which travels to the brain through the bloodstream. GDF15 is rapidly inducible by acute physical, biochemical, and mental stressors, and GDF15 increases exponentially with age (upper left box, data from <sup>167</sup>), outlining factors that must be considered when designing and interpreting human studies. Other metabolites (e.g., lactate, a signal of reductive stress) and proteins (e.g., FGF21) can act as mitoception signals under certain conditions. *Efferent arm:* In response to GDF15, the brain deploys a dual i) energy conservation and ii) energy mobilization strategy, shutting down acutely-dispensable energy expensive physiological processes, and recruiting energy substrates from energy stores. Through mitoception, the brain monitors and regulates the balance between cellular energy demand and mitochondrial transformation capacity. Evidence and action of signals may act at different scales (lower left box).

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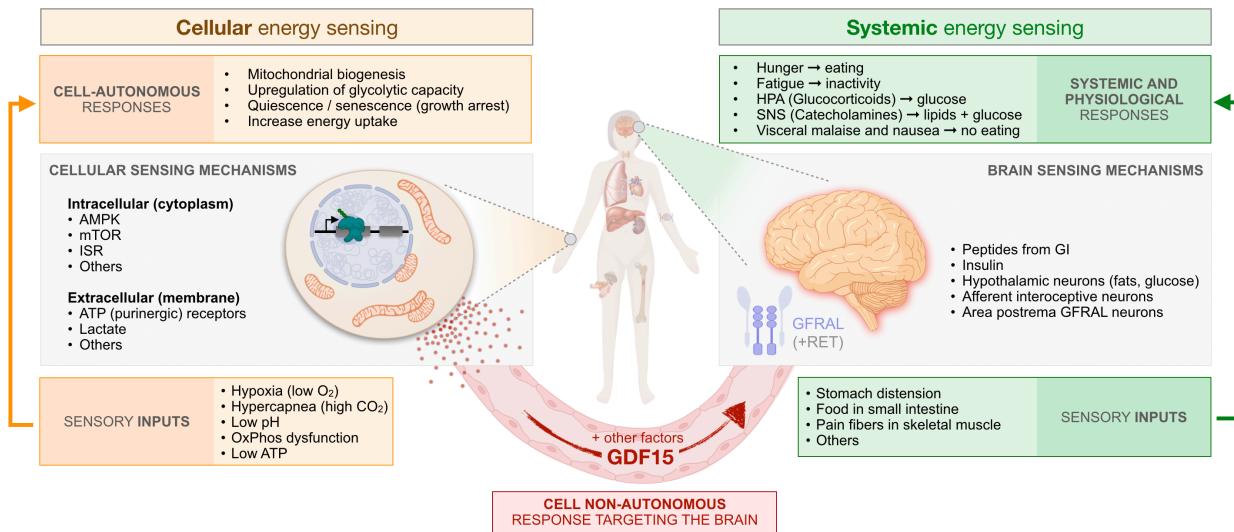
### **Conflict of interest**

The authors have no competing interests to declare.

### **Author contributions**

C.C.L., Q.H., E.D.S., C.T., M.P. conceptualized and contributed to the literature review. C.C.L. and M.P. prepared the figures. E.E., T.D.W., D.W.B., L.F.B., A.A.C. and M.Z.W. critically revised the manuscript. All authors reviewed the final version manuscript.

## Box 1. Intracellular and systemic inter-organ energy sensing mechanisms.



**INTRACELLULAR ENERGY SENSING.** Cells sense energy levels in a cell-autonomous manner via intracellular sensors such as AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), NAD<sup>+</sup>-dependent sirtuins, and the integrated stress response (ISR). These molecular sensors capture intracellular levels of energy intermediates such as ATP and its lower energy versions ADP/AMP, or the redox ratio NAD<sup>+</sup>:NADH. To operate harmoniously as an organism, cells must also sense the energetic state of their surrounding cells. Thus, most cells express cell surface receptors for extracellular ATP and other metabolic intermediates such as lactate<sup>46,168</sup>, which allows cells to sense the status of the shared “social” space between the cell collective<sup>49</sup>. Such signals from the cytoplasm or the cell surface are then transmitted to the cell nucleus where they mobilize the appropriate gene expression programs evolved to enhance cellular fitness. These programs can induce cell-autonomous recalibrations, including mitochondrial biogenesis (the production of additional mitochondria) and upregulate other metabolic pathways, or involve the secretion of cytokines such as GDF15 and interleukins, to alert other cells of their energy deficiency (Figure, left).

**INTER-ORGAN COMMUNICATION.** The brain also senses systemic energy levels. In dedicated brain regions, specialized neurons sense glucose and fatty acids from the surrounding bloodstream, subsequently activating downstream circuits that orchestrate hormone secretion, metabolic activities, and food seeking behaviors<sup>1,2,8,169-171</sup>. Sensors scattered in blood vessels near the heart and in the brain detect the vital gases: oxygen (O<sub>2</sub>, the primary substrate for mitochondrial energy transformation) and CO<sub>2</sub> (the primary by-product of respiration)<sup>172</sup>. Both low O<sub>2</sub> and high CO<sub>2</sub> are key signals of low energy status. The emotional salience and physical discomfort (i.e., panic from asphyxiation) of oxygen deficiency and excess CO<sub>2</sub> reflect the vital importance of these signals for our biology – running out of fuel for mitochondria would be the end of both the body and mind.

The brain also senses signals from the stomach (ghrelin) and the small intestine (GLP-1, CCK) to regulate food seeking/eating relative to other organismal priorities over short periods of time (hours, days)<sup>1</sup>, whereas signals from adipocytes (leptin)<sup>173</sup> allows organism to regulate energy intake and expenditure over long time periods (weeks, months). Immune cell cytokine signals are also sensed by the brain to facilitate reallocation of energetic resources from behavior and active energy expenditure towards fighting infection (sickness behavior)<sup>5</sup>, and skeletal myocytes signal via myokines (e.g. IL6) to inform the brain of activity intensity relative to aerobic fitness<sup>16</sup>. This set of endocrine inter-organ communication system forms an interoceptive network, signaling the abundance or scarcity of energy resources. In response to

signals of energy deficiency, the brain also has multiple mechanisms to translate these signals into conscious experiences (e.g., hunger, fatigue) and physiological responses that promote survival in the face of energy scarcity. (Figure, *right*). Converging intracellular and brain-based systemic metaboceptive mechanisms have evolved to sense and respond to the scarcity of energetic resources, both in the short and long-term.

## **Box 2. Empirical approaches and considerations to elucidating GDF15 psychobiology**

Defining the role of GDF15 in linking psychosocial factors, fatigue, and other energetic challenges will require the following types of studies:

1. **Large-scale epidemiology.** Large datasets with multidimensional biological and psychosocial variables can be used to test whether GDF15 statistically mediates the relationship between exposures (e.g. exercise, sleep deprivation, injury, immune challenges) on outcomes variables of interest, such as fatigue and anxiety. Strengths of this approach include the ability to control for numerous confounders (e.g., age, sex, SES status); limitations include the cross-sectional nature of data and the occasional imperfect timing of biological and psychosocial measures.
2. **Longitudinal observational.** Studies with repeated measures of GDF15 and/or psychosocial variables can reveal meaningful temporal associations pointing to the impact of energy gaps on psychosocial, psychiatric and clinical outcomes, and vice versa.
3. **Clinical studies with greater temporal resolution.** Studies measuring GDF15 at a scale of minutes to hours are necessary to temporally and accurately relate changes in GDF15 to changes in mood, physiology, symptoms, and/or complex behaviors.
4. **Controlled clinical interventions.** To determine the specific and direct effects of GDF15 on mood, physiology, symptoms, and/or complex behaviors, controlled studies involving psychological, behavioral or pharmaceutical interventions are required.
5. **Mechanistic studies of GDF15 signaling.** To establish if GDF15 is sufficient and necessary to mediate the effects of cellular energy gaps on organismal functions, mechanistic studies involving cell-based *in vitro*, *in vivo* in animal models may be required. Human studies using neutralizing antibodies to block body-to-brain GDF15 signaling<sup>165</sup> are valuable.

Some technical and conceptual considerations for investigating GDF15 psychobiology include:

1. **Age.** GDF15 displays an unusually strong ( $r_s=0.5-0.8$ , depending on the age range examined) exponential relationship with age<sup>36,167</sup>. Computing the residual of GDF15 exponentially regressed onto age (log GDF15 linearly regressed to age) or using partial correlation between log GDF15 and the variable of interest, adjusting for age, can account for this effect.
2. **GDF15 variants.** In the *1000 Genome Project* 23% of the population carried the H202D GDF15 variant<sup>174</sup> (estimated to be ~15-30% of global populations). This variant is under-detected by the commonly used R&D ELISA kit when compared to the Roche Elecsys assay<sup>175</sup>. When measuring GDF15, the limitations of the method and possibility of under detection should be considered.
3. **Pregnancy.** Given the ~200-fold increase in blood GDF15 with pregnancy<sup>84</sup>, pregnancy is an important confounder that must be objectively assessed.
4. **Diurnal GDF15 patterns.** Given evidence of diurnal variation in some animals<sup>87,88</sup> and humans studies<sup>89,106</sup>, GDF15 should be systematically measured at specific times of day.
5. **GDF15 stability.** Some analytes degrade progressively with storage time. Evidence of GDF15 stability with cryostorage is limited, but it is fair to assume at least moderate protein stability since it is reliably quantified even after ~5-20 years of storage via proteomics<sup>39</sup>, ELISA<sup>61</sup>. Storage time could possibly be a covariate in longitudinal studies.
6. **Safety.** In mechanistic human studies, manipulating GDF15 levels could have unanticipated side-effects. However, GDF15-deficient individuals appear phenotypically normal when under basal conditions<sup>176</sup>, and neutralizing endogenous GDF15 appears well-tolerated<sup>165</sup>. Treatment with recombinant GDF15 did not cause well-known unanticipated major problems, but the short half-life of GDF15 (3 hours in monkeys)<sup>177</sup> and the poor tolerability due to gastrointestinal disorders (nausea and vomiting) should be considered<sup>143,178</sup>.

## OUTSTANDING QUESTIONS

- Is GFRAL expression exclusively confined to area postrema brain neurons, or are other GDF15 receptors expressed in other cell types in peripheral (non-brain) organs?
- Does GDF15 play a role in wound healing, sleep, or other restorative processes?
- How do biological/physiological variables including hormones, metabolic, immune, and other blood biomarkers contribute to regulate baseline and stress-reactive GDF15?
- Does circulating GDF15 exhibit diurnal regulation? If so, what is the magnitude and pattern relative to other neuroendocrine and metabolic factors?
- Do chronic psychosocial stressors such as loneliness, adversity, workplace stress, discrimination and others elevate circulating GDF15?
- Do interventions that increase well-being, including mindfulness, relaxation, psychedelic-assisted therapy, and others decrease circulating GDF15?
- How robust are blood and saliva GDF15 as markers of psychosocial stress compared to cortisol and other *bona fide* stress hormones? What are the dynamics and effect sizes of GDF15 changes after psychological stress in different populations (ages, sex, health status, etc.)?
- What transdiagnostic features of psychopathology (e.g., anhedonia) relate to circulating GDF15 in depression, anxiety, PTSD, schizophrenia, and other mental illnesses?
- Can vicarious experiences of stress and pain, or well-being, influence GDF15?
- Is there a reliable brain signature of systemic energy gaps reflected in elevated circulating GDF15? Is this signature responsive to interventions and the healing process that resolve energy gaps?
- Does GDF15 constrain mood and the emotional state space of possible human experiences? Is GDF15 associated with valence emotions?

**Table 1. Empirical rationale for examining GDF15 levels in relation to positive and negative psychosocial factors linked to increased fatigue in human studies**

Psychosocial construct		Evidence related to fatigue
<b>NEGATIVE</b>	Chronic stress	↑ fatigue with caregiver stress <sup>179</sup> ↑ fatigue with job-related stress <sup>180</sup>
	Depression	↑ frailty in elderly (Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scales) <sup>160</sup> ↑ fatigue <sup>181</sup>
	Anxiety	↑ frailty in elderly (Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scales) <sup>160</sup> ↑ mental fatigue in healthcare workers during COVID19 <sup>182</sup>
	Psychological distress	↑ frailty in elderly w increased PSS (Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scales) <sup>160</sup> ↑ frailty in elderly <sup>183</sup>
	PTSD	↑ mental fatigue in healthcare workers during COVID19 <sup>182</sup> ↑ fatigue in healthcare workers <sup>184</sup>
	Burnout & workplace stress	↑ fatigue <sup>185,186</sup>
	Loneliness	↑ fatigue <sup>187,188</sup> ↑ fatigue, ↓ energy (n.s.) <sup>189</sup>
	Early life adversity (ELA)	↑ fatigue <sup>181</sup>
<b>POSITIVE</b>	Social support	↓ fatigue during COVID19 lockdown (mediated by stress, worry, COVID19 worries) <sup>190</sup>
	Mindfulness	↓ fatigue <sup>181</sup> ↓ fatigue in perimenopausal women <sup>191</sup>
	Optimism	↓ fatigue <sup>192</sup>

**Table 2. Preliminary associations between psychosocial, behavioral and fatigue-related traits, and mental illnesses, and GDF15 in the UK Biobank.**

TRAITS ASSOCIATED WITH GDF15	GDF15 effect direction	Effect size ( $\beta$ ) [95%CI]	SE	P-value
<i>Feelings of fatigue</i>				
Waking unrefreshed severity over the past week	↑	0.26 [0.19-0.33]	0.035	$4.00 \times 10^{-14}$
Recent feelings of tiredness or low energy	↑	0.24 [0.16-0.30]	0.036	$6.86 \times 10^{-11}$
Feeling tired or having little energy over the last two weeks	↑	0.32 [0.25-0.39]	0.038	$8.81 \times 10^{-20}$
<i>Physical impairments/impairments to daily life</i>				
Mobility problems today	↑	0.45 [0.37-0.52]	0.030	$9.74 \times 10^{-30}$
Self-care problems today	↑	0.47 [0.37-0.58]	0.053	$7.21 \times 10^{-19}$
Problems doing usual activities	↑	0.39 [0.28-0.43]	0.038	$5.74 \times 10^{-21}$
<i>Social/Physical Activities</i>				
Sports and social activities attended in person at least once a week_	↓	-0.27 [-0.95- -0.18]	0.043	$5.89 \times 10^{-10}$
Sports club or gym or fitness class				
Types of physical activity in the last 4 weeks_	↓	-0.35 [-0.38- -0.31]	0.020	$1.83 \times 10^{-69}$
Walking for pleasure (not as a means of transport)				
Liking taking the stairs	↓	-0.24 [-0.41- -0.29]	0.031	$1.61 \times 10^{-28}$
Sports and social activities attended in person at least once a week_	↓	-0.27 [-0.95- -0.18]	0.043	$5.89 \times 10^{-10}$
Sports club or gym or fitness class				
<i>Negative psychosocial states</i>				
Neuroticism score	↑	0.12 [0.08-0.18]	0.018	$3.53 \times 10^{-11}$
PREVALENT DISEASES	GDF15 effect direction	OR [95%CI]	P value	
Smoking dependency	↑	2.60 [2.15-3.15]		$5.01 \times 10^{-23}$
Alcohol dependence	↑	2.24 [1.87-2.69]		$1.50 \times 10^{-18}$
Substance abuse, excluding more controls	↑	2.18 [1.94-2.45]		$8.14 \times 10^{-39}$
Any mental disorder	↑	2.16 [1.99-2.34]		$3.08 \times 10^{-80}$
Mood disorders, excluding more controls	↑	2.15 [1.94-2.37]		$8.78 \times 10^{-51}$
Depression or dysthymia	↑	2.02 [1.81-2.26]		$9.88 \times 10^{-36}$
Alcohol use disorder, ICD-based	↑	2.02 [1.74-2.35]		$1.50 \times 10^{-20}$
Depression	↑	1.96 [1.77-2.17]		$6.20 \times 10^{-37}$
Schizophrenia or delusion, excluding more controls	↑	1.94 [1.61-2.33]		$3.20 \times 10^{-12}$
Mental and behavioural disorders due to alcohol, excluding acute intoxication	↑	1.90 [1.66-2.17]		$3.68 \times 10^{-21}$
Anxiety disorders, excluding more controls	↑	1.65 [1.40-1.93]		$9.06 \times 10^{-10}$

Data from the UK Biobank atlas of plasma proteins (Deng et al. Cell 2025, <https://proteome-phenome-atlas.com/>), which examined 2,920 plasma proteins in relation to disease prevalence and incidence (406 prevalent and 660 incident) as well as 986 health-related traits in 53,026 individuals. Associations between plasma proteins and health-related traits were assessed using linear regression for continuous traits (as outcome) and binary traits (as exposures), while proportional odds logistic regression was applied for ordered categorical traits. All regressions were performed with the adjustment of participants' baseline information of age, sex, ethnicity, Townsend deprivation index, Body-Mass Index (BMI), smoking status, fasting time, season of blood collection (summer/autumn: June to November versus winter/spring: December to May) and blood age (date of blood collection to date of protein examination).

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