

# Hyperinsulinaemia as a cause of obesity and cardiometabolic diseases

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## Abstract

This narrative Review explores the role of hyperinsulinaemia as a potential independent contributor to obesity and cardiometabolic diseases. We argue that scientific discussions about the role of hyperinsulinaemia as a causal factor in these conditions have not sufficiently distinguished between postprandial insulin excursions and chronically elevated basal levels of insulin. We summarize findings from observational and experimental human trials, as well as preclinical models, and outline how reasonable evidence suggests that chronic (basal) exposure to elevated levels of insulin, rather than normal postprandial insulin excursions in isolation, might have a role in promoting or exacerbating the development of adiposity. We discuss the putative contributors to hyperinsulinaemia, including genetic predisposition, early-life influences, diet, environmental pollutants and physical inactivity, highlighting causality knowledge gaps relevant to the prevention of obesity and cardiometabolic diseases.

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## Key points

- The duration of continuous exposure to increased levels of insulin might be a critical factor in determining the pathogenic effects of insulin, with fasting (basal) insulin probably serving as a useful proxy of 24-h insulin exposure.
- Evidence from both observational and experimental studies suggests that long-term basal insulin exposure contributes to weight gain and adiposity, but evidence for postprandial insulin exposure is lacking.
- Hyperinsulinaemia might independently influence cardiometabolic diseases such as type 2 diabetes mellitus and cardiovascular disease via routes such as inflammation and insulin resistance; however, conclusive evidence is limited.
- Environmental pollutants, physical inactivity and early life nutritional exposures are plausible drivers of increased basal levels of insulin.

## Introduction

The prevalence of obesity has tripled since 1975, with current data estimating that ~2 billion people (39% of the global population) have overweight or obesity<sup>1</sup>. Obesity, a term we use here as a proxy for excess adiposity, is a major risk factor for morbidity and mortality, including cardiometabolic conditions and obesity-related cancers, among many other diseases, and is associated with considerable stigma, which can cause further harm to the physical and mental health of those affected<sup>2,3</sup>. Preventing and treating obesity offers an opportunity to improve health for billions of people, reducing the burden on our healthcare systems and society while also improving the lives of those affected by this complex health condition.

During the past half century, large transformations in our living environments and sociodemographic changes have occurred, including widening economic and social inequalities and a reduction in physical activity, as well as increases in sedentary behaviours<sup>4</sup>, food intake outside the home<sup>5–7</sup> and consumption of ultra-processed convenience foods<sup>8</sup>. While the rapid rise in obesity over the past five decades can largely be attributed to the increased energy intake and positive energy balance that results from the interplay of these environmental and sociodemographic drivers<sup>9</sup>, the effect of these factors on the weight of individuals is heterogeneous (Fig. 1). Various biological factors can modify the effect of environmental factors on body weight, including: genetics<sup>10</sup>, basal metabolic rate<sup>11</sup>, hormonal changes<sup>12</sup> and exposures in utero (such as exposure to energy restriction or hyperglycaemia)<sup>13</sup>. Notably, considerable discordance can occur between the presence of obesity per se and the development of obesity-related diseases<sup>14,15</sup>, which suggests that genetics and biological factors influence the degree of vulnerability towards the deleterious effects of excess adiposity. It is also important to appreciate that there is increasing evidence for the existence of multiple phenotypic and genetic subtypes of obesity<sup>16,17</sup>, each of which varies in the relative weighting of its causal factors and in the range of associated comorbidities<sup>18,19</sup>. Clearly, understanding obesity and its related comorbidities and diseases extends beyond the concept of energy balance.

Here, we examine the role of insulin (an anabolic hormone that also has antilipolytic effects) in energy homeostasis. Specifically, we focus on hyperinsulinaemia as an independent driver of obesity and

related comorbidities, placing it in the context of the obesogenic environment (Fig. 1). The relationship between hyperinsulinaemia and the pathogenesis of obesity and its complications has attracted much debate<sup>20,21</sup>, in particular the causal role of dietary carbohydrate in driving high levels of insulin secretion and thus obesity<sup>22</sup>. Our view is that the distinction between physiological postprandial insulin excursions and chronically elevated basal levels of insulin has been overlooked in this debate, and is important because the mechanisms for basal insulin secretion differ from those for feeding-related rapid rises in levels of glucose<sup>23</sup>. If fasting levels of insulin are low and postprandial levels of insulin are elevated, the exposure of the tissues to so-called high levels of insulin might be transient if oral intake of insulinogenic stimuli such as carbohydrate or protein is infrequent, such as three meals per day. Conversely, if fasting levels of insulin are elevated, insulin concentrations could remain elevated for 24 h per day, as any excursion will be rising from an already elevated concentration of insulin (Fig. 2). Thus, physiological postprandial insulin excursions do not necessarily reflect 24-h insulin exposure.

Furthermore, although hyperinsulinaemia is tethered to insulin resistance<sup>24</sup> (and the terms are often used interchangeably), in this article we focus on the former (defined by elevated circulating concentrations of insulin per se), rather than the more heterogeneous term insulin resistance, whose definition might depend on the tissue-specific and substrate-specific action of insulin. However, we refer to tissue-specific or pathway-specific presentation of insulin resistance where relevant. We also emphasize the challenges of quantifying highly dynamic insulin concentrations and the wider limitations of the evidence base. We also summarize the state of the evidence on potential causes of hyperinsulinaemia, including nutritional and environmental secretagogues, and identify the key research gaps.

## A causal role for hyperinsulinaemia Hyperinsulinaemia and the development of obesity

Hyperinsulinaemia is a general term for an absolute or relative elevation of insulin concentration in blood. However, to our knowledge, there is no current agreed definition, clinical or otherwise, of hyperinsulinaemia, and different cut-off values for elevated insulin are also used in the literature<sup>25–27</sup>. At present it is not known (other than in recognized clinical conditions such as insulinomas) at what concentration, and for what duration, insulin becomes pathological. Furthermore, in contrast to established international standards for glucose and other clinical risk factors, difficulties with the standardization of assays for insulin (and its surrogate C-peptide) limit comparisons between studies or cohorts<sup>28</sup> and hinder establishment of robust cut-off values for defining hyperinsulinaemia. Moreover, measured insulin concentrations in the fasting state are pulsatile and variable, adding an additional challenge in studies that seek to determine the relationship between fasting insulin concentration and any outcome.

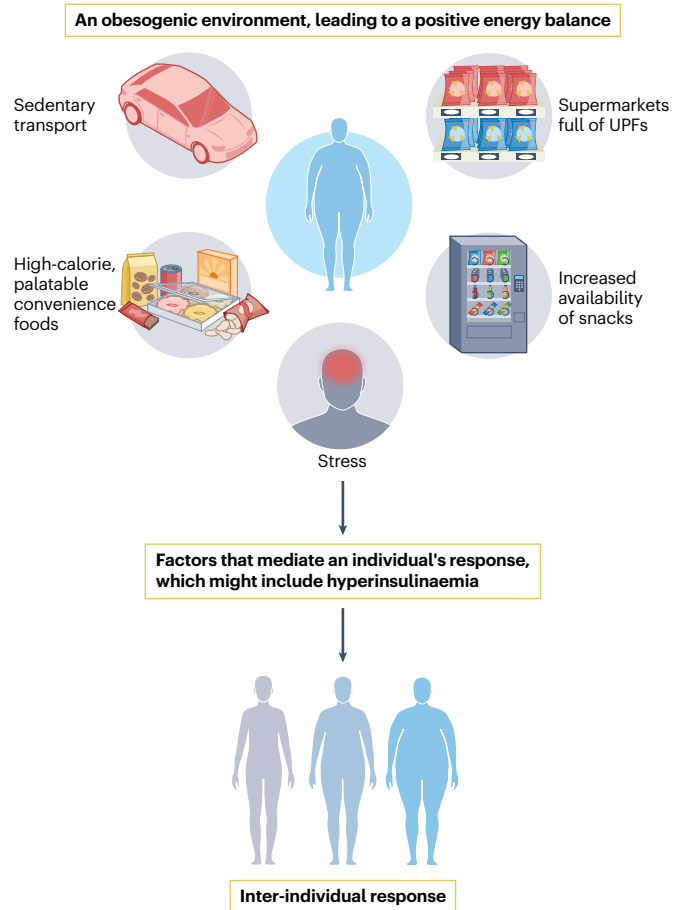
Nevertheless, we can draw some preliminary conclusions from the observational and experimental literature regarding the role of insulin in the development of obesity and its related diseases. For example, prospective observational studies have found that fasting hyperinsulinaemia precedes the development of obesity in children<sup>29–31</sup>, and people who are insulin hypersecretors have greater adipose tissue mass in cross-sectional and follow-up studies than those who are non-hypersecretors (the term ‘hypersecretors’ is defined as the upper tertile of the distribution of the residuals of the best-fit line between total insulin secretion rate and whole-body insulin sensitivity index during a 3-h oral glucose tolerance test)<sup>32,33</sup>, although this effect is not

always observed<sup>34</sup>. Notably, these data come from studies in which hyperinsulinaemia was not accompanied by overt hyperglycaemia. In adults, some studies have shown no relationship between fasting levels of insulin and weight change over a 6-year period<sup>35</sup>, whereas other data suggest that baseline fasting levels of insulin can predict weight gain over 10 years<sup>36</sup>. It is worth noting that the first study was limited to adults above the age of 50 years without diabetes mellitus, whereas the latter study was based on the National Health and Nutrition Examination Survey population and included a wider age range and participants with normoglycaemia, prediabetes and type 2 diabetes mellitus (T2DM). However, in observational studies, insulin and weight change contemporaneously, and it is difficult to determine which causes which<sup>37</sup>. Causality can be addressed with genetic and Mendelian randomization studies, but the pleiotropic effect of genes makes these studies hard to interpret<sup>38–40</sup>. However, monogenic variants that lead to insulin hypersecretion (validated by an *in vitro* knockdown model) are associated with increased birthweight, which suggests a causal role for insulin in body weight<sup>41,42</sup>.

Causality can also be addressed with highly controlled experimental studies, such as those in preclinical animal models in which insulin levels are specifically reduced (Table 1). A series of studies in mice with genetically reduced insulin production have shown that hyperinsulinaemia is causally related to diet-induced weight gain and adiposity<sup>12,43</sup>. Similarly, reducing insulin levels in mice that have already gained adipose tissue is sufficient to cause adipose depot-specific weight loss<sup>44</sup>. In each of these experiments, the genetically altered mice have altered fasting levels of insulin but fairly normal insulin responses to glucose challenge, which suggests that insulin exposure over a 24-h (chronic) timescale is important.

In human trials, experimental reductions in insulin concentrations with the use of pharmaceuticals (diazoxide or octreotide) have resulted in greater weight loss than placebo<sup>45–48</sup>. The effect of these drugs is to decrease both fasting and postprandial insulin levels, meaning that 24-h exposure to insulin is decreased. A different trial using diazoxide showed no effect on weight loss<sup>49</sup>; however, in this trial, no difference in insulin levels at the end point at 8 weeks was seen between the group receiving diazoxide and the group receiving placebo. These studies are not without their limitations. For example, diazoxide has effects on lipid metabolism that might be independent of insulin<sup>50</sup>, and octreotide increases plasma levels of glucose and thus loss of glucose through the urine<sup>46</sup>. Octreotide can also cause weight gain following bariatric surgery, which is associated with the suppression of satiety hormone secretion<sup>51</sup>. Despite these limitations, subgroup analysis shows a close relationship between suppression of insulin and weight loss<sup>45</sup>. Conversely, basal insulin therapy led to a small but statistically significant increase in weight of 1.3 kg compared with 0.5 kg weight loss with conventional stepped therapy using an oral agent in people with prediabetes or early T2DM (median baseline HbA<sub>1c</sub> was 6.4%) in whom reversal of glycosuria-mediated loss of calories is likely to be negligible<sup>52</sup>. Collectively, these clinical data, including short-term inhibition and long-term addition of insulin, support the view that insulin *per se* has some role in weight change.

Dietary interventions have also been used to test the causal role of insulin on obesity<sup>53</sup>. A very low-carbohydrate (ketogenic) diet lowered both fasting and postprandial insulin levels<sup>54,55</sup> compared with a control diet with a higher carbohydrate component, but had no effect on adiposity for up to 4 weeks. However, the ketogenic diet also significantly increased circulating levels of free fatty acids (FFAs) creating a distinct metabolic milieu, in contrast to the suppression or absence

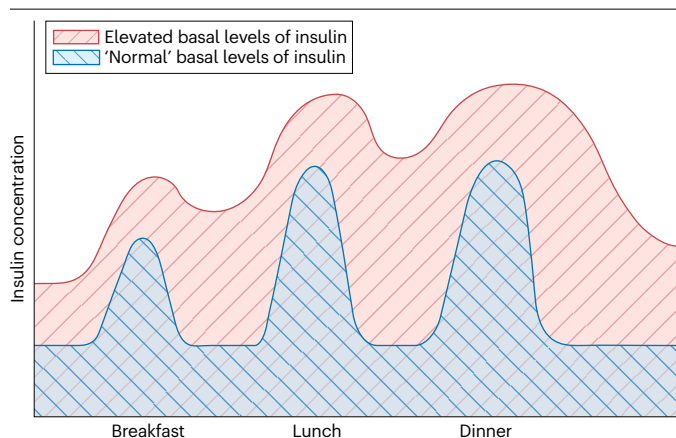


**Fig. 1 | Contextual overview of the role of hyperinsulinaemia in obesity and related conditions at the population level.** The obesogenic environment primarily drives population-level obesity, but factors such as hyperinsulinaemia contribute to an individual's susceptibility to that environment. UPFs, ultra-processed foods.

of change in levels of FFAs alongside the genetically reduced insulin secretion in rodent studies or as a result of treatment with diazoxide in humans<sup>12,48,50</sup>. A 2021 meta-analysis of longitudinal studies and 26 randomized clinical trials of heterogeneous interventions, including dietary and pharmaceutical interventions, found that decreases in fasting levels of insulin were more likely to precede decreasing weight than the reverse<sup>56</sup>.

Overall, our interpretation of the available evidence is that basal (fasting) and 24-h exposure to increased insulin concentrations might contribute to the development of obesity. Thus, the duration of continuous exposure to elevated insulin concentrations (Fig. 2) might be a key factor determining the obesogenic effects of insulin. We emphasize that although the magnitude of the effect might be small, accumulation over time might still be an important contributor to the prevalence of obesity at the population level, and the effect might be greater in some people than in others (Fig. 1).

Few data are available on the independent effects of transient postprandial insulin excursions on obesity. Isolating the effects of fasting from the those of postprandial insulin can be difficult and is made more complex by the heterogeneous influence of genetic traits on insulin dynamics<sup>57</sup>. For example, in a Mendelian randomization



**Fig. 2 | Example of basal levels of insulin.** Postprandial insulin response on a background of 'normal' basal insulin compared with elevated 24-h insulin exposure driven by high basal levels of insulin in the context of chronic hyperinsulinaemia. Note that there is currently no agreed diagnostic cut-off value for normal versus pathological insulin concentrations.

study<sup>38</sup> that aimed to examine the relationship between genetic variants associated with postprandial insulin levels, some of the variants used (*HHEX* single nucleotide polymorphism rs1111875) were not found to be associated with insulin release during an intravenous glucose tolerance test<sup>58</sup>, and some are associated with both elevated basal and glucose-stimulated insulin secretion<sup>59</sup>. Although we could try to draw conclusions from pharmaceutical trials of drugs that differentially affect fasting (basal) and postprandial insulin levels, interpretation of these trials is not straightforward for several reasons: any drug used for the treatment of hyperglycaemia in T2DM will alter energy balance (for example, by reducing loss of glucose in the urine); the occurrence of hypoglycaemia might alter eating behaviours; and many of these drugs have off-target effects. More refined experimental methods than those currently available will be needed to understand what effect, if any, excessive postprandial insulin excursions might have on the development of obesity.

In summary, although the evidence base is complex and with many limitations, our interpretation is that 24-h (basal) insulin exposure might have a role in driving adiposity but that this cannot be simply assumed from the postprandial insulin response to isolated food intake and/or meals, and might be dependent on the frequency of meals and the length of the eating window.

## Hyperinsulinaemia and the development of cardiometabolic diseases

The same limitations that apply to the evidence base about the link between hyperinsulinaemia and obesity also apply to the development of cardiovascular disease (CVD), alongside additional complexities. First, if hyperinsulinaemia is causing obesity, then obesity per se will increase the risk of diseases such as T2DM and CVD (Fig. 3). Determining whether hyperinsulinaemia increases the risk of such diseases independently of obesity is incredibly challenging. Some evidence does suggest that overall insulin exposure might be related to CVD independently of BMI. For example, in the Swedish Obesity Subjects study, a greater relative treatment benefit was seen in participants with high baseline fasting levels of insulin than in those with low fasting levels

of insulin, whereas baseline BMI did not modify the treatment effects<sup>60</sup>. Additionally, a positive relationship has been observed between very high insulin dosage and cardiovascular mortality and major adverse cardiovascular events<sup>60,61</sup>. Evidence also supports a bidirectional relationship between fasting levels of insulin and abdominal obesity<sup>37,62</sup>, and if hyperinsulinaemia increases central adiposity, it also probably increases the risk of cardiometabolic disease.

The clinical pathways through which insulin might increase CVD risk are not fully clear. For example, although insulin modulates the regulatory pathways involved in blood pressure<sup>63,64</sup>, short-term experimental studies that increase basal insulin concentrations via intravenous infusion have not found consistent evidence that hyperinsulinaemia causes hypertension<sup>65–68</sup>. Similarly, short-term studies have not demonstrated that hyperinsulinaemia causes dyslipidaemia<sup>69,70</sup>. However, these types of experimental studies usually last a matter of hours or days. Many of the biological pathways that lead to dyslipidaemia, hypertension and atherosclerosis operate on much longer exposure timelines. In this context, it is relevant to note that common and rare variations in the *INS* and *INSR* genes, which would influence both basal and postprandial insulin concentrations over the long-term, are associated with blood pressure and hypertension-related traits<sup>71</sup>, and a Mendelian randomization study found causal evidence for the role of hyperinsulinaemia in CVD<sup>72</sup>.

Consistent and strong causal evidence indicates that hyperinsulinaemia impairs insulin-stimulated glycogen synthase activity and glycogen synthesis, and also causes  $\beta$ -cell dysfunction. These effects were seen after as little as 20 h of exposure, with an increase in basal insulin in each of the studies<sup>73–76</sup>. As these pathways are unequivocally related to the development of T2DM, a causal role for hyperinsulinaemia in the development of T2DM seems self-evident (Fig. 3). A study published in 2023 also found greater adipose tissue accrual and a threefold higher risk of abnormal glucose tolerance at the 2-year follow-up in individuals identified as primary insulin hypersecretors at baseline compared with those classified as normal insulin secretors<sup>33</sup>.

Many chronic diseases are characterized by inflammation (Fig. 3), which itself causes impairment in key metabolic signalling pathways. In humans, experimentally inducing hyperinsulinaemia can increase circulating levels of cytokines<sup>77,78</sup>. Furthermore, in rodent models, hyperinsulinaemia stimulates expression of cytokines in adipose tissue whereas experimental reduction in insulin levels decreases the macrophage content in adipose tissue<sup>79</sup>. Subtle changes in whole-body insulin signalling pathways (caused by exposure to chronically elevated insulin levels and inflammation) might promote the eventual development of hypertriglyceridaemia or hypertension<sup>80,81</sup>. Thus, there are multiple potential pathways through which hyperinsulinaemia could drive the long-term development of cardiometabolic diseases (Fig. 3), but the evidence is not conclusive.

## Causes of hyperinsulinaemia

Insulin levels can become elevated as a result of excessive insulin secretion, reduced insulin clearance or a mixture of both. The most common view has been that chronic hyperinsulinaemia represents a normal response of healthy pancreatic  $\beta$ -cells increasing their insulin production and secretion to compensate for whole-body insulin resistance. Clear evidence demonstrates that this view is oversimplified: underfeeding (fasting) improves hepatic insulin sensitivity but increases peripheral insulin resistance, whereas insulin secretion decreases<sup>82</sup>. Conversely, overfeeding impairs hepatic insulin sensitivity with no effect on peripheral insulin sensitivity, and insulin secretion (and thus

insulin concentrations) increase<sup>83</sup>. Therefore, insulin secretion can respond to rises in circulating levels of glucose or fats (that is, the need to store excess fuel) and a hypercaloric diet raises fasting levels of insulin within 24 h<sup>83–85</sup>. Hence, it is no surprise that there is a strong association between obesity and fasting hyperinsulinaemia. In this context, hyperinsulinaemia occurs as a result of overfeeding and thus might exacerbate weight gain (Fig. 1). However, evidence also suggests that in some people insulin hypersecretion occurs before hepatic insulin resistance or any other explanatory cause is present<sup>32,73,86,87</sup>. If ‘primary’ over-secretion of insulin is widespread, there would be major implications for how we should consider obesity development and prevention.

In addition, impaired insulin clearance might also be a cause of hyperinsulinaemia. We refer readers to other excellent reviews on the subject<sup>88,89</sup>, but note that although some studies show that the rate of hepatic extraction adjusts to insulin secretion and action<sup>90,91</sup>, others suggest that these two aspects of insulin biology are not always coupled<sup>45,92,93</sup>. In addition, there seem to be differences in insulin clearance rates between people of different ethnicity, which suggests that reduced insulin clearance might be an acquired trait<sup>94</sup>.

## Potential causes of ‘primary’ hyperinsulinaemia

### Non-modifiable causes

**Age.** It is not clear whether there is an association between age and fasting insulin concentrations, with some cohorts suggesting there is a decrease in fasting levels of insulin, and others suggesting an increase in fasting levels of insulin with age<sup>95,96</sup>. The inconsistent data might be due to confounding by the effects of age per se on body composition, genetic differences influencing  $\beta$ -cell mass or proliferation, or the effects of environmental exposures (such as dietary factors, physical activity or environmental pollutants).

**Genetic causes.** Evidence from genome-wide association studies indicates that T2DM risk genes are typically involved in insulin secretion, which strongly suggests that there is a genetic component driving defects in insulin secretion<sup>97</sup>. Although some genetic variants are associated with reduced insulin secretion<sup>98</sup>, others are associated with elevated fasting levels of insulin<sup>99</sup>. Work is ongoing to understand how genetic variants could drive insulin hypersecretion, and the metabolic consequences of insulin hypersecretion<sup>42</sup>.

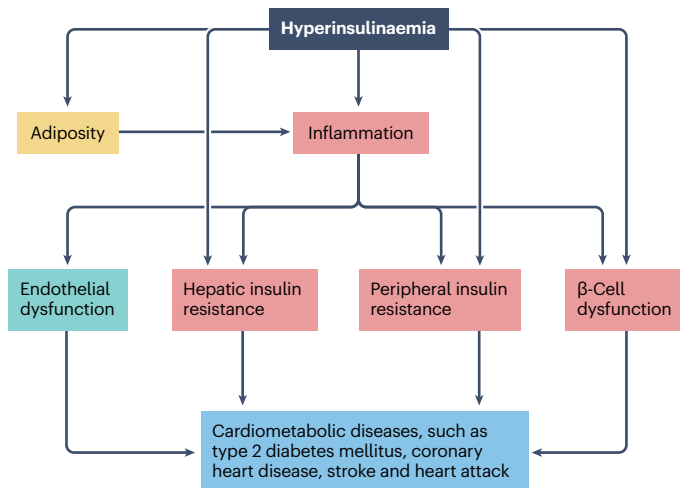
### Modifiable causes

**Early life drivers.** The intrauterine environment is known to influence lifelong health<sup>13</sup>, and evidence from human observational studies and non-human primate cohorts indicates that in utero exposure to hyperglycaemia and hyperlipidaemia could increase fasting levels of insulin into childhood<sup>100,101</sup>. This effect might be the result of the insulin secretory characteristics of the islet being altered, although definitive evidence on hypersecretion is lacking<sup>102</sup>. Epigenetic changes that cause over-proliferation of  $\beta$ -cells and elevated fasting levels of insulin might partly explain phenotypic variation in body composition<sup>103</sup>. The postnatal period might also alter the lifelong insulin secretory potential of the  $\beta$ -cells. In human trials, the use of formula with a lower protein content (consistent with that of breast milk) during the first year of infancy led to a lower BMI at 2, 6 and 11 years of age compared with children given formula during infancy with a higher protein content<sup>104,105</sup>. These findings agree with observational findings that high protein intake early in life is associated with greater adiposity throughout childhood<sup>106</sup>. Infants consuming high-protein diets have higher fasting levels of insulin and insulin-like growth factor 1 than infants consuming lower protein diets, which could potentially explain the increase in adiposity<sup>107</sup>.

**Table 1 | Preclinical evidence for a conserved causal role for insulin in adiposity**

Model	Insulin change	Outcome
<b>Direct manipulations of fasting levels of insulin</b>		
HFD male <i>Ins1<sup>-/-</sup>;Ins2<sup>-/-</sup></i> versus <i>Ins1<sup>+/+</sup>;Ins2<sup>-/-</sup></i> mice	Complete prevention of diet-induced fasting hyperinsulinaemia at 1 year	Complete prevention of diet-induced weight gain, adipocyte hypertrophy and fatty liver <sup>43</sup>
HFD female <i>Ins1<sup>-/-</sup>;Ins2<sup>+/+</sup></i> versus <i>Ins1<sup>-/-</sup>;Ins2<sup>+/+</sup></i> mice	Transient near-complete reduction of fasting hyperinsulinaemia at 25 weeks	Prevention of diet-induced weight gain at 25 weeks of age with sustained effect <sup>12</sup> ; protection from fatty liver and increased lifespan <sup>12,169</sup> ; phenotype reversed with Insulin 2 peptide released via a minipump <sup>12</sup>
HFD male <i>Ins1<sup>-/-</sup>;Ins2<sup>lox/+</sup>;Pdx1Cre<sup>ER</sup></i> versus <i>Ins1<sup>-/-</sup>;Ins2<sup>lox/+</sup></i> mice	~40% lower fasting levels of insulin, no change in stimulated insulin	20–30% reduced gonadal and perirenal adipose tissue mass (percent body mass) 5 weeks after deletion <sup>44</sup>
High sugar-fed <i>Drosophila</i> after deleting insulin-producing cells	~50% reduction in insulin	~30% reduced body adipose; phenotype reversed by adding back insulin gene <sup>170</sup>
10–14-day insulin infusions (multiple routes) in adult male Wistar rats	~30% increase in fasting levels of insulin	~20–30g more weight gain compared with mice receiving saline <sup>171</sup>
7-day subcutaneous insulin infusion in 18-week-old C57BL6/J female mice	Not measured	~10% increase in body weight; ~30–40% increased adipose tissue weight <sup>172</sup>
<b>Indirect effects on fasting levels of insulin</b>		
HFD male $\beta$ -cell-specific <i>Glud1</i> -knockout mice	~50% lower fasting levels of insulin	~50% less weight gain, epididymal adipose pad weight; consistent phenotype with acute deletion <sup>173</sup>
HFD male $\beta$ -cell-specific <i>Cask</i> -knockout mice	~20% lower fasting levels of insulin	Improved insulin resistance; statistically significantly increased insulin signalling in adipose tissue <sup>174</sup>
HFD male $\beta$ -cell-specific <i>Abcb10</i> -knockout mice	~20% lower fasting levels of insulin	Improved insulin resistance <sup>175</sup>

The table provides details of models with genetically modulated insulin in the context of a hyperinsulinaemia-inducing high-fat diet, the degree of circulating insulin reduction and the physiological outcomes. HFD, high-fat diet.



**Fig. 3 | Direct and indirect pathways through which hyperinsulinaemia might increase cardiometabolic risk.** Hyperinsulinaemia might directly lead to inflammation, hepatic and peripheral insulin resistance and  $\beta$ -cell dysfunction. Inflammation itself also contributes to endothelial dysfunction, hepatic and peripheral insulin resistance and  $\beta$ -cell dysfunction. Endothelial dysfunction, hepatic and peripheral insulin resistance and  $\beta$ -cell dysfunction in turn lead to cardiometabolic diseases. This simplified schematic does not include the many metabolic intermediates regulating these processes.

**Dietary factors.** Further to the demonstrable effect of a hypercaloric diet on increasing fasting levels of insulin<sup>83–85</sup>, eucaloric dietary factors also change insulin secretion and clearance rates, and might thus theoretically cause hyperinsulinaemia.

Despite the potent meal-time insulinogenic effect of carbohydrate and protein, the evidence does not suggest that either a diet high in starchy carbohydrate or high in protein raises fasting levels of insulin<sup>54,108–115</sup>. Marked reductions in carbohydrate alongside an increase in dietary fats lower fasting levels of insulin in the short term (3 days to 6 weeks) by increasing insulin clearance<sup>55,116–118</sup>, but also lead to an increase in levels of FFAs, which theoretically could promote hyperinsulinaemia in the long term, at least in susceptible individuals<sup>119,120</sup>. Diets high in indigestible carbohydrates (particularly fermentable fibre) lower fasting levels of insulin without increasing FFA concentrations, with data suggesting that increased insulin clearance is the likely mechanism<sup>121–124</sup>. Consumption of the monosaccharides and disaccharides fructose and sucrose (composed of glucose and fructose) at high concentrations (for example, ~25% of kcal per day) might lead to elevated fasting levels of insulin when such consumption replaces glucose or starch<sup>125,126</sup>; however, this effect has not been seen in all studies<sup>127,128</sup>, and might have been influenced by baseline insulin status<sup>126</sup>. In addition, the Western diet has changed in striking ways in the past 30 years and now largely comprises ultra-processed foods, which are low in fibre and contain thousands of novel food ingredients. A strong mechanistic rationale and preclinical work<sup>129</sup> suggest that some food additives could be generating false autocrine and endocrine metabolic signals, including generation of reactive oxygen species (ROS) that impair the body's energy regulatory systems<sup>130</sup>. For example, monoglycerides are widely added to commercial food products and stimulate basal insulin secretion in rat pancreatic  $\beta$ -cells and the clonal  $\beta$ -cell line INS-1 832/13 (ref. 131).

Trial data for most sweeteners (such as aspartame, acesulfame K and stevia) do not show an increase in fasting levels of insulin up to about 12 weeks<sup>132–134</sup>. However, sucralose consumption does increase fasting levels of insulin after 2 weeks and 12 weeks<sup>135–137</sup>, with impaired insulin clearance identified as a potential mechanism<sup>138</sup>. Of note, other studies showed no effect of sucralose after similar levels of exposure<sup>139,140</sup>. It is possible that the effect of sweeteners on insulin secretion or clearance might be affected by other nutrients that they are consumed with<sup>141</sup>, previous exposure and/or by interindividual differences such as the microbiome<sup>136</sup>.

In summary, a combination of reduced intake of fibre and whole foods alongside increased and widespread ingestion of novel food ingredients could be a contributor to hyperinsulinaemia in the population.

**Environmental pollutants.** Similar to food additives<sup>130</sup>, humans are also exposed to chemicals in the environment that can be internalized and might predispose an individual to obesity. These so-called obesogens include solvents, pesticides, clothing and furniture protectants, personal care products and other chemicals. Exposure can occur via air, water, food, skin contact or dust inhalation. Persistent organic pollutants (POPs) are of particular concern because they are lipophilic and highly stable, resulting in bioaccumulation; POPs are detectable in populations even in remote regions of the globe<sup>142</sup>. Human exposure to POPs (as determined by circulating concentrations) consistently correlates with clinical measures of insulin secretion<sup>143,144</sup> and T2DM risk<sup>145</sup>. Moreover, the concentration of POPs measured within human pancreas tissue samples positively correlates with high basal insulin secretion in isolated islets from the same donors (according to findings published in a preprint paper)<sup>146</sup>. Emerging experimental evidence also demonstrates a direct causal link between exposure to POPs and dysregulated  $\beta$ -cell function<sup>147</sup>.

Not all environmental pollutants are lipophilic or persistent. For example, chemicals found in plastics, such as bisphenols (for example, bisphenol A (BPA) and BPA replacements) and phthalates are metabolized and excreted quickly; these chemicals are consistently detected in human urine, which is indicative of ubiquitous exposure<sup>148</sup>. Observational data in humans show a link between high urinary BPA concentrations and elevated fasting levels of insulin<sup>149</sup>. Experimental trials in humans show impairment in the first-phase and second-phase insulin secretory response following administration of BPA<sup>150</sup>. Extensive evidence from rodent studies also demonstrates that BPA and BPA alternatives disrupt insulin secretion<sup>151</sup>.

Many potential modes of action could explain how obesogens in our environment cause hyperinsulinaemia<sup>147,151</sup>. Some environmental chemicals directly target receptors that act as nuclear transcription factors, such as the aryl hydrocarbon receptor, in pancreatic islets<sup>152</sup>. Many obesogens increase ROS production<sup>153</sup> in vitro and in animal models<sup>130</sup>. Excessive ROS production increases basal insulin secretion via mechanisms in the  $\beta$ -cell that mimic overnutrition<sup>131</sup>. Exposure to these obesogens might also indirectly lead to an increase in fasting levels of insulin via impaired insulin signalling in adipose tissue and hepatic tissue and induction of inflammatory pathways<sup>154</sup>. It is also important to note that obesogens might also influence weight gain via insulin-independent mechanisms<sup>153</sup>. In summary, it is highly plausible that chronic low-dose exposure to exogenous chemicals contributes to basal hypersecretion of insulin and obesity.

**Physical activity and exercise.** The modernization in societies and changes in the built environment have engineered physical activity out

of the lives of many people. Worldwide, 31% of the population is physically inactive, defined as engaging in <150 min of moderate-intensity activity per week. Exercise (muscle contraction) promotes muscle glucose uptake via insulin-independent mechanisms, an effect linked to recruitment of exercise-responsive GLUT4 transporters during each bout of exercise, which dissipates early in recovery (that is, within minutes)<sup>155</sup>. Accordingly, the effects of exercise in reducing prevailing or chronic hyperinsulinaemia are probably mediated by the effects of acute and chronic exercise in improving insulin sensitivity. Aerobic-based exercise reduces the insulin area under the curve in response to an oral glucose load following a single bout<sup>156</sup> and several weeks<sup>157,158</sup> of training, and insulin responses to meals are lower on days when participants are active compared with those when they are sedentary (lengthy sitting)<sup>159,160</sup>. Meta-analyses of supervised training studies in normoglycaemic adults<sup>161</sup> and individuals living with T2DM<sup>162</sup> have shown lowered fasting concentrations of insulin and HOMA-IR in the trained compared with control conditions. By contrast, 7 days of forced sedentary behaviour in regular exercisers leads to an increase in fasting and postprandial insulin concentrations, an effect attributed to reduced hepatic insulin extraction<sup>163</sup>.

Taken together, these data suggest that exercise can lower 24-h exposure to insulin as a result of both reduced insulin secretion and increased hepatic insulin extraction<sup>92,164</sup>, and preclinical studies have highlighted plausible molecular mechanisms<sup>165</sup>. Collectively, these data suggest that the well-known benefits of physical activity in reducing chronic disease risk might be attributable, at least in part, to reductions in exposure to (or risk of) hyperinsulinaemia. Whether this effect is secondary to improved insulin sensitivity, increased hepatic insulin extraction and/or the myriad of other metabolic effects of exercise (for example, muscle and liver glycogen turnover) remains to be determined.

## Implications and research needed

Based on our review of the literature, our interpretation is that there is reasonable evidence that hyperinsulinaemia, reflected most accurately as elevated basal and/or fasting levels of insulin, has a small causal and/or exacerbating role in the global rise in obesity. Although the effect size might be small, over time the cumulative effect and interaction of several identified drivers of chronic hyperinsulinaemia might exacerbate the effect of a positive energy balance on obesity. Higher quality evidence, including the integration of mechanistic studies with observational data and human clinical trials, is needed to better understand a causal role for hyperinsulinaemia in obesity. If chronically elevated levels of insulin are causally linked to obesity and associated cardiometabolic disorders, it has critical implications for our public health response. For example, if ubiquitous environmental pollutants or food additives are contributing to a rise in obesity, then regulation must happen. Likewise, we would need to acknowledge the role of the built environment in driving our inactivity and contributing to weight gain via its effects on hyperinsulinaemia. Finally, we would need to urgently address intrauterine and early life nutrition so we are not 'stacking the deck' against the health of our children.

We believe that experimental studies are needed in four key research areas: manipulating insulin concentrations in humans; the effects of intrauterine and early life nutrition on insulin secretory capacity, insulin concentrations and adiposity later in life; the effects of common nutritional additives and environmental chemicals on insulin secretion; and measurement of 24-h insulin concentrations.

## Manipulating insulin concentrations in humans

The strongest trials are experimental studies that manipulate insulin concentrations, ideally in the most direct manner possible. Although the data are compelling in rodents, off-target effects of insulin inhibitors limit the conclusions we can draw from the trials performed in humans to date. Identification and use of more precise inhibitors of insulin secretion would help strengthen the evidence that hyperinsulinaemia is causal in the development of obesity. The use of intravenous insulin infusions to mimic varying magnitudes of postprandial insulin excursions could also help fill the gap in understanding what role, if any, postprandial excursions have in increasing adiposity.

## Effects of intrauterine and early life nutrition

The intrauterine and postnatal periods, and childhood and adolescence, are key windows when the endocrine pancreas is functionally maturing and expanding to reach an appropriate adult  $\beta$ -cell mass. In humans at 30 years of age, very little  $\beta$ -cell proliferation occurs and physical  $\beta$ -cell mass is mainly determined by the survival of existing  $\beta$ -cells. As such, it is likely that early nutritional intake has a larger effect on  $\beta$ -cell development and lifelong insulin secretory capacity than nutrition in later life, by which time the  $\beta$ -cell capacity has been set. A variety of rodent studies, human trials and observational studies in humans (with frequent measurement of insulin throughout early life) will be needed to improve our understanding in this critical area of research.

## Effects of common nutritional additives and environmental chemicals

Given the ubiquity of novel compounds both in food and in the environment, combined with experimental and epidemiological data suggesting that they are related to insulin concentrations or T2DM incidence<sup>130,136,166</sup>, further research should investigate the effect of these compounds on insulin secretion and clearance. Given the daunting number and diversity of chemicals in our environment, high-throughput approaches using reliable *in vitro* models are needed to help prioritize chemicals that should be studied in more detail. Immortalized rodent  $\beta$ -cell lines are typically used for toxicology studies<sup>147</sup>, but we advise caution in assuming the translatability of these findings<sup>167</sup>. Although all currently available *in vitro*  $\beta$ -cell models have limitations, we encourage the use of primary islets or stem cell-derived islets as tools for assessing the effect of environmental chemicals on insulin secretion<sup>168</sup>. Stronger evidence than is currently available from both *in vitro* and *in vivo* experimental studies will help determine what compounds, if any, need to be regulated.

## Measurement of 24-h insulin concentrations

Our inability to continuously measure insulin under free-living conditions limits our understanding of how 24-h exposure to hyperinsulinaemia affects the risk of obesity and related diseases. Although the gold standard for establishing causality will be experimental studies (in which either the insulin concentration or the exposure to dietary or environmental factors is manipulated), observational studies that can capture long-term exposure to environmental or nutritional factors alongside (frequent) measurement of 24-h insulin concentrations will help complete the picture of the long-term real-world effect of these exposures. Such studies are currently limited by the need to bring individuals into a laboratory or clinical setting to take a blood sample for measurement of insulin. Some of these studies use laboratory-based postprandial insulin responses from oral glucose tolerance testing to define postprandial hyperinsulinaemia, which might not reflect

day-to-day postprandial levels of insulin in response to actual meals. Methods to measure insulin or C-peptide concentrations (for example, in dry blood spot, interstitial fluid and saliva samples) at multiple time points throughout the day (for example, fasting, interprandial and 3 h after a meal) and/or assess chronic exposure (for example, urinary levels of C-peptide) could provide some insight into insulin exposure in large observational studies.

## Conclusions

Although the obesogenic environment is the primary driver of increased adiposity at the population level, other factors clearly have an influence on an individual's risk of obesity. We believe reasonable evidence indicates that chronic exposure to increased levels of insulin, but not physiological postprandial insulin excursions, could drive or exacerbate obesity. Basal levels of insulin, currently best reflected by fasting concentrations of insulin, might be a reasonable surrogate for chronic insulin exposure. It is currently not entirely clear what could be causing excessive basal insulin secretion; however, plausible environmental exposures and behaviours have been identified. We believe research in this area should be prioritized and we have made specific recommendations for how to advance this important area of study.

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## Author contributions

N.G., J.D.J., A.V., A.A.T., B.C., J.E.B. and J.P.L. researched data for the article. N.G., J.D.J., A.V., A.A.T., B.C., J.E.B. and J.P.L. contributed substantially to discussion of the content. N.G., J.D.J., A.V., A.A.T., B.C., J.E.B. and J.P.L. wrote the article. N.G., J.D.J., A.V., A.A.T., B.C. and J.P.L. reviewed and/or edited the manuscript before submission.

## Competing interests

N.G. has previously consulted for Heartland Food Products Group, who make the artificial sweetener sucralose. J.D.J. is a paid consultant for Abcellera, a Vancouver-based biotech, on an unrelated project. At the time of writing the manuscript, A.A.T. was an employee and shareholder of Novo Nordisk. Novo Nordisk had no role in the writing of the manuscript. J.P.L. holds founders shares in Metabolic Insights Inc., a company developing non-invasive metabolic monitoring devices. The other authors declare no competing interests.

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