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EXTENDED ARTICLE

Impact of overweight and obesity on fasting insulin secretion in men and women without diabetes: effect sizes and mechanisms

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Abstract

Aims/hypothesis Fasting hyperinsulinaemia is a key feature of obesity and is implicated in diabetes progression. However, the following aspects of insulin secretion remain unclear: (1) which index of obesity is most important; (2) what is the shape of the dose–response curve between obesity and insulin secretion; (3) what physiological mechanisms sustain insulin hypersecretion; (4) what are the underlying causes; and (5) whether sex-related differences exist.

Methods We analysed data from 1250 healthy participants (547 men, 703 women) of the EGIR-RISC cohort followed up for 3.5 years, with age 30–60 years and BMI 18.5–40.0 kg/m^2. Assessments included body composition, insulin secretion, beta cell function modelling from an OGTT and clamp-derived insulin sensitivity. Endogenous glucose production (EGP) was measured in a subset of 368 participants. Multivariable regression models and stratifications for BMI, body fat per cent, WHR and fat mass were applied to evaluate the effect of obesity on insulin secretion and beta cell function.

Results The impact of obesity on fasting insulin secretion (FIS) was continuous across the full spectrum of BMI and WHR values and was greater in men than women. Among adiposity indices, fat mass (standardised β coefficient [Stβ] 0.27, $p<0.0001$) and waist circumference (Stβ 0.21, $p<0.0001$) were the strongest predictors of FIS. Insulin secretion increased 2.4-fold across BMI deciles, and adiposity-associated insulin hypersecretion appeared to be driven by the combination of hyperglycaemia and an increase in a specific beta cell function variable (insulin secretion rate at 5 mmol/l glucose [ISR@5]). In the follow-up cohort, weight gain (mean ± SD Δ weight=+5.1 ± 3.8 kg) was associated with an increase in FIS and fasting glucose (+0.20 ± 0.63 mmol/l, $p<0.03$), whereas weight loss (−4.7 ± 2.8 kg) led to a reduction in FIS and fasting glucose (+0.06 ± 0.55 mmol/l, $p<0.006$). ISR@5 declined in both weight losers and those with stable weight (−0.17 ± 1.9 and −0.16 ± 1.0 U/h, respectively; $p<0.002$ for both) but not in weight gainers (−0.06 ± 1.1 U/h). Peripheral insulin resistance, plasma NEFA and leptin accounted for only part of obesity's effect on insulin secretion. Subset analysis of fasting and clamp EGP data suggested a rightwards shift in the dose–response curve across fat mass quintiles, indicating progressive hepatic glucose overproduction despite a preserved hepatic insulin response.

Conclusions/interpretation The effect of body mass on insulin secretion is continuous, more pronounced in men, driven by fat mass and waist, sustained by hyperglycaemia and by an upregulation of beta cell insulin secretion and is only partially explained by typical hormonal and metabolic consequences of obesity. We suggest that hepatic glucose overproduction contributes to the fasting hyperinsulinaemia observed in individuals with obesity.

Keywords Adiposity · Beta cell function · Insulin · Obesity

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSA	Body surface area
EGIR-RISC	European Group for the Study of Insulin Resistance - Relationship between Insulin Sensitivity and Cardiovascular Disease
EGP	Endogenous glucose production
FFM	Fat-free mass
FIS	Fasting insulin secretion
FISn	FIS normalised for BSA
FPG	Fasting plasma glucose
IGT	Impaired glucose tolerance
ISR@5	Insulin secretion rate at 5 mmol/l glucose
LogW	Logworth false discovery rate
Stβ	Standardised β coefficient

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Research in context

What is already known about this subject?

- Fasting hyperinsulinaemia is a key feature of obesity and is implicated in the progression of type 2 diabetes
- The relationship between different indices of obesity and fasting insulin secretion (FIS) is not well defined
- The physiological mechanisms sustaining insulin hypersecretion and potential sex-related differences remain unclear

What is the key question?

- What are the major drivers and physiological mechanisms underlying obesity-related fasting insulin hypersecretion, and are there sex-related differences?

What are the new findings?

- The effect of obesity on FIS was near-linear, primarily driven by fat mass and waist circumference, and was more pronounced in men
- Insulin hypersecretion was sustained by increased plasma glucose levels and beta cell function upregulation, rather than solely by metabolic consequences of obesity
- Hepatic glucose overproduction was observed in individuals with obesity despite a preserved hepatic response to insulin, suggesting a contributing role in fasting hyperinsulinaemia

How might this impact on clinical practice in the foreseeable future?

- Understanding the role of hepatic glucose overproduction and beta cell adaptation in obesity-related hyperinsulinaemia may help refine strategies for early intervention in obesity-related metabolic disorders

Introduction

Primary insulin hypersecretion is associated with negative metabolic consequences in both adults and children, as we have recently described [1, 2]. In this study, we aimed to elucidate the mechanisms responsible for the control of fasting insulin secretion (FIS) in men and women, with a focus on obesity, which is the most important driver of hypersecretion [3], and on the fasting state, whose complex regulation is substantially different from the post-load condition [4].

Indeed, several aspects of FIS are still unclear. The shape of the dose–response curves for indices of body mass expansion (from lean to obese) and insulin secretion is still poorly defined; even less understood is the extent to which the effect of adiposity on insulin secretion differs between men and women, given the substantial sex-related differences in the size, distribution and biology of adipose tissue [5]. This lack of clarity also applies to the mechanisms sustaining beta cell hypersecretion in people with overweight/obesity; specifically, the relative contribution of hyperglycaemia vs a gain in beta cell function remains ill defined.

With regard to the aetiology, the existing paradigm is that obesity, by inducing skeletal muscle and liver insulin resistance, imposes additional insulin secretion to restrain glucose production and increase glucose utilisation [6, 7]. However, muscle insulin resistance explains only a limited portion of the inter-individual variability of fasting insulin levels [3] and glucose utilisation in fasting conditions is largely non-insulin-dependent [8]. Moreover, liver insulin resistance is not a consistent finding in obesity [9, 10], and it is evident only at minute systemic insulin concentration gradients above normal fasting values [11], which is likely irrelevant in obesity, a condition characterised by high fasting portal concentrations [10].

Thus, other factors beyond insulin resistance are likely to contribute to the inter-individual variability of FIS and they are potentially related to differences in fat depot size and biology, and/or to the metabolic liver's adaptation to obesity. Interestingly, in response to a diet-induced modest weight loss, endogenous glucose production (EGP) in individuals with type 2 diabetes remains remarkably stable, while fasting insulin declines to a significant extent [12], suggesting other mechanisms of control.

Another key methodological aspect, rarely considered, concerns the normalisation of insulin secretion. Normalising insulin secretion for body mass or body surface area, as typically done, could underestimate the burden that obesity imposes on the beta cell population. In fact, with obesity, beta cell mass expands to some extent, although not in direct proportion to body mass. As shown by Saisho et al [13], a doubling of BMI (from 20 kg/m^2 to

40 kg/m^2) was associated with a 50% increase in beta cell mass in individuals without diabetes. Therefore, reporting absolute insulin secretion (in pmol/min) does not require assumptions, and produces more clinically meaningful data.

In the present analysis, we have addressed these issues by analysing the European Group for the Study of Insulin Resistance - Relationship between Insulin Sensitivity and Cardiovascular Disease (EGIR-RISC) cohort of men and women without diabetes (n=1250; BMI range 18.5–40.0 kg/m^2) who underwent extensive metabolic phenotyping and were followed for 3.5 years [14].

Methods

Participants The RISC study was a prospective, observational study conducted across 19 centres in Europe in 2004–2010. The study initially included 1566 healthy participants at baseline, of whom 1059 attended the 3.5 year follow-up visit, which included metabolic testing with a 2 h 75 g OGTT and measurements of adiposity indexes. For the present analyses, data were used from 1250 participants (547 men [44%] and 703 women [56%]) at baseline and from 1016 participants with available follow-up data, selected according to the following inclusion criteria: age 30–60 years, BMI 18.5–40 kg/m^2, BP <140/90 mmHg and no diabetes (fasting plasma glucose [FPG] <7.0 mmol/l or OGTT 2 h plasma glucose <11.0 mmol/l). Exclusion criteria were as follows: weight change of ≥5 kg in the past 6 months; any malignancy within the last 5 years; pregnancy; chronic cardiovascular, lung, kidney or liver disease as reported by participants or their physicians; and chronic steroid therapy [14]. At each centre, the recruitment followed a homogenous age strata sampling. Sex was recorded as male or female (biological sex), while gender identity was not collected. Data on race/ethnicity were not collected in the RISC study, which is broadly representative of middle-aged adults of European origin.

Study approval All participants gave their written informed consent prior to recruitment. The study was conducted according to the principles expressed in the Declaration of Helsinki and approved by the local ethics committee at each centre.

Anthropometric measurements Standardised procedures were used to collect anthropometric data such as height, waist circumference and WHR. Baseline body weight and composition were assessed using electrical bioimpedance with the Tanita TBF-300 scale (Tanita International Division, UK), measuring fat mass (kg), fat-free mass (FFM, kg), and percentage of fat mass (fat%), calculated as the ratio of fat mass to total body weight. Body surface area (BSA) was calculated using the Gehan & George method: BSA (m^2)=weight (kg)$^{0.51456}$ × height (cm)$^{0.42246}$ × 0.0235 [15].

Metabolic tests Following an overnight fast, participants underwent a 2 h OGTT with blood samples collected for glucose, insulin and C-peptide at baseline, 30, 60, 90 and 120 min post-glucose ingestion. Impaired glucose tolerance (IGT) was identified by 2 h plasma glucose levels between 7.8 and 11.0 mmol/l. FIS was derived from C-peptide deconvolution [16] and expressed in U/h (using the conversion factor 6 pmol=1 mU). Fasting insulin clearance was calculated as the ratio between insulin secretion rate and serum insulin levels in fasting conditions and expressed in l/min.

On a separate day, all participants underwent a standardised hyperinsulinaemic–euglycaemic clamp study with exogenous insulin infused at a rate of 240 pmol min^{-1} m^{-2}, alongside a variable 20% dextrose infusion adjusted every 5–10 min to maintain plasma glucose within 0.8 mmol/l (±15%) of the target. Blood samples were collected every 20 min during the clamp to measure insulin and C-peptide concentrations.

In 368 individuals, EGP was measured in the fasting state and during the clamp with a tracer technique using D-[6–6^{2}H$_2$]glucose and expressed both as μmol min^{-1} kg$_{FFM}^{-1}$ as previously described [17], as well as in g/h (using the conversion factor 1 μmol=180 μg).

Clamp hepatic insulin sensitivity was then calculated by plotting the fasting and clamp (during the final 20 min of the test [18]) EGP values vs the corresponding sinusoidal insulin concentrations, which were log-transformed to account for the typical non-linear kinetics of insulin action on the liver.

Portal insulin concentration in the fasting state was estimated from C-peptide-derived insulin secretion rate (by deconvolution [16]) assuming a portal venous blood flow of 487 ml min^{-1} m^{-2} [19]. Clamp portal insulin concentration was calculated as the plasma insulin concentration, achieved by the exogenous infusion, plus the C-peptide-derived endogenous insulin secretion that is diluted in the portal venous blood flow. Sinusoidal insulin was calculated assuming that arterial blood flow contributes to 20% of total (arterial plus portal) liver perfusion [19].

Blood glucose levels were determined using the glucose oxidase method at the bedside during the metabolic tests, as well as through centralised biochemical analyses, to reduce assay errors and variability. Serum insulin and C-peptide concentrations were assessed using a fluoroimmunoassay (AutoDELFIA Insulin kit; Wallac, Turku, Finland) conducted in a centralised laboratory. NEFA were measured by a fluorometric method (Wako, Neuss, Germany) as previously detailed [20]. Plasma leptin was measured with an in-house time-resolved immunofluorometric assay (AutoDELFIA autoanalyzer; Wallac) in a central laboratory (Medical Research Laboratories, Clinical Institute and Medical Department, Aarhus University Hospital, Aarhus, Denmark).

Beta cell function modelling Beta cell function was assessed using the OGTT plasma C-peptide and glucose data and

a validated mathematical model described previously [21]. This model characterises the relationship between insulin secretion and glucose concentration using three components: (1) beta cell glucose sensitivity, which measures the dependency of insulin secretion on absolute glucose concentration via a dose–response function, whose value at a fixed glucose level of 5 mmol/l is identified by the insulin secretion rate at 5 mmol/l of plasma glucose (ISR@5); (2) this dose–response is adjusted to account for the potentiation phenomenon, which includes modulation of the dose–response by both glucose and non-glucose factors (e.g. prolonged hyperglycaemia, gastrointestinal hormones and neurotransmitters); and (3) beta cell rate sensitivity, which accounts for the dependence of insulin secretion on the rate of change in glucose concentration and is a marker of early insulin release. For the purpose of this study, we only used the estimate of ISR@5, which provides a measure of fasting beta cell secretion that is not affected by the inter-individual variability of FPG.

Statistical analysis Variables with normal distributions are presented as mean ± SD; others are presented as median with IQR. Categorical variables are expressed as percentages. To represent the variations of metabolic variables across the whole spectrum of adiposity, we divided the cohort into sex-specific deciles of BMI, fat% and WHR and graphically reported the interpolation curves resulting from the cubic polynomial fit of the mean data with its 95% CI. To evaluate the effect of each adiposity index and sex across the deciles, we used a multivariable model that included sex alone and the interaction term with the adiposity index. To establish a hierarchy among obesity indices, we incorporated them into multivariable linear regression models (including age, sex and interaction terms) and reported the standardised β coefficient (Stβ). The false discovery rate, logworth FDR (LogW), is also reported in our final multivariate analysis to allow a more accurate ranking of each variable effect. Complete case analysis was used to address missing data. Statistical analyses were conducted using JMP Pro software, version 16.0.0 (SAS Institute, Cary, NC, USA), with a two-sided α level of 0.05. Graphical representations were generated using GraphPad Prism, version 8.0.0 (GraphPad Software, La Jolla, CA, USA).

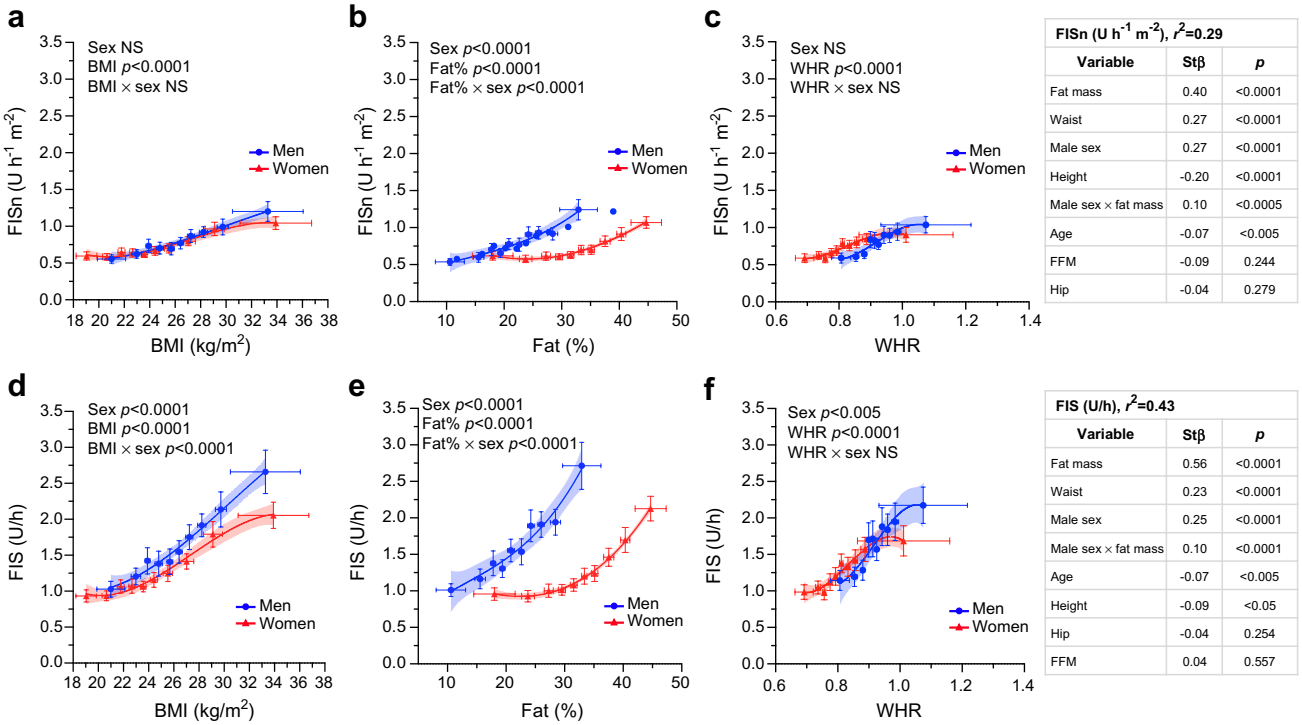
Results

Characteristics of the study population In the whole cohort, the prevalence of participants with normal weight (BMI 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obesity (30–39.9 kg/m^2) was 50%, 37% and 13%, respectively. The overall prevalence of IGT was 8.6%, with the expected gradient across classes of BMI (5.3, 10.7 and 16.5%, respectively). As shown in electronic supplementary material (ESM) Table 1, in both men and women, lean individuals (i.e. in the first two or three BMI deciles) were slightly younger (by 2–3 years), while age remained similar across higher BMI deciles. In men, height did not differ across BMI deciles, whereas in women, higher BMI deciles were associated with a slightly shorter stature (by 2–3 cm). The weight gradient between the extreme BMI deciles was 37 kg in men and 40 kg in women. The fat% in women was almost double that in men across all BMI deciles, showing a twofold increase between the extreme deciles in both sexes. Fat mass was similar in men and women, with a fourfold increase between the extreme deciles. WHR was higher in men than in women but both sexes displayed a similar gradient across BMI deciles. FFM increased linearly in both men and women but only to a limited extent, reaching a maximum increase of 22%. Alanine aminotransferase (ALT) levels increased progressively across BMI deciles, while aspartate aminotransferase (AST) remained unchanged. As expected, the typical features of the insulin resistance syndrome (hyperinsulinaemia, lower insulin sensitivity, higher BP, lower HDL-cholesterol and higher triglycerides) gradually emerged across deciles of BMI.

Relationship between indices of obesity and FIS FIS normalised for BSA (FISn, Fig. 1) increased with BMI and WHR, in a continuous quasi-linear fashion, similarly in men and women, with no clear threshold. Overweight, expressed as fat%, displayed a continuous and steep relationship with FISn in men, while in women the relationship was initially flat and increased above 30% (fat% × sex interaction, $p<0.0001$, Fig. 1). The curves between FIS and all obesity indices (BMI, fat%, and WHR) were steeper when insulin secretion was not normalised for BSA (Fig. 1); across deciles of BMI, non-normalised FIS increased by 2.4-fold while FISn increased by 1.9-fold.

In a multivariate analysis using only the primary anthropometric variables (fat mass, FFM, waist and hip circumferences, height) together with sex and age (Fig. 1), fat mass and waist circumference were the strongest independent predictors of FIS, along with male sex alone and in interaction with fat mass. The pattern was similar regardless of normalisation, although, a larger fraction of the overall variance was explained when insulin secretion was not normalised (Fig. 1).

The close relationship between fat mass and FIS, and the sex-related differences, can also be appreciated from simple linear regression analysis, which yielded similar r^2 values (0.37 in both men and women), but different slopes (0.065 in men and 0.040 in women) (ESM Fig. 1). Among women, 167 (13%) were postmenopausal. The slopes of the fat mass–FIS relationship did not differ between pre- and postmenopausal women (ESM Fig. 2), indicating that menopausal status did not significantly modify this association.



FISn (U h^{-1} m^{-2}), r^2=0.29

Variable	Stβ	p
Fat mass	0.40	<0.0001
Waist	0.27	<0.0001
Male sex	0.27	<0.0001
Height	-0.20	<0.0001
Male sex × fat mass	0.10	<0.0005
Age	-0.07	<0.005
FFM	-0.09	0.244
Hip	-0.04	0.279

FIS (U/h), r^2=0.43

Variable	Stβ	p
Fat mass	0.56	<0.0001
Waist	0.23	<0.0001
Male sex	0.25	<0.0001
Male sex × fat mass	0.10	<0.0001
Age	-0.07	<0.005
Height	-0.09	<0.05
Hip	-0.04	0.254
FFM	0.04	0.557

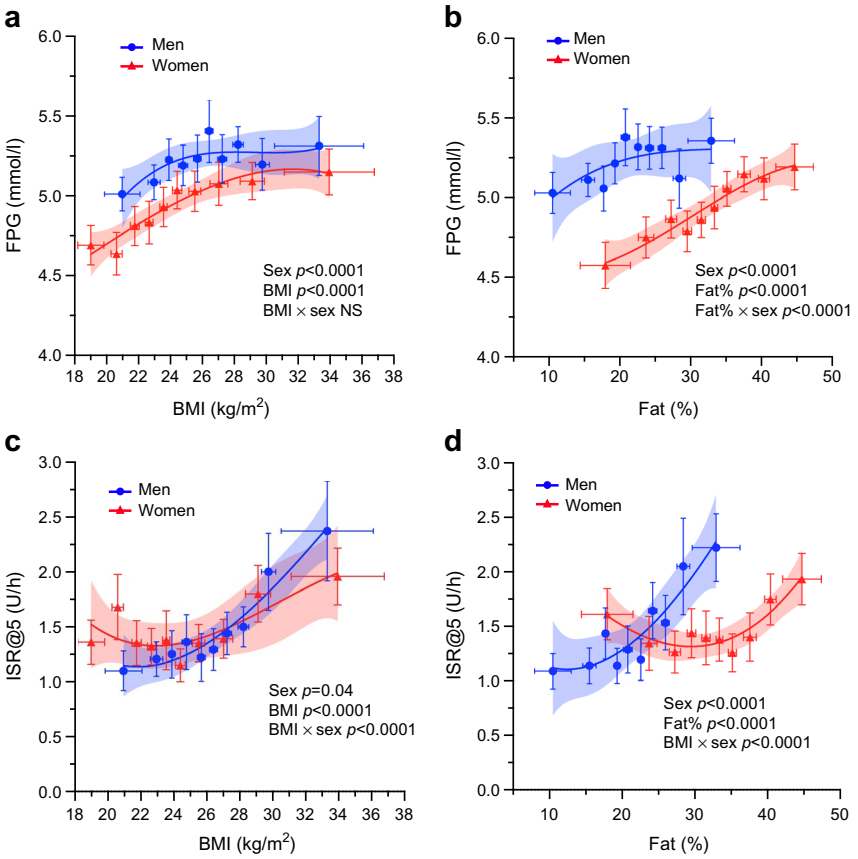
Fig. 1 Polynomial third-order fit of the mean data of FISn (**a**–**c**) and non-normalised insulin secretion (FIS, **d**–**f**) across sex-specific deciles of three different obesity indices (BMI [**a**, **d**], fat% [**b**, **e**] and WHR [**c**, **f**]) in men (blue) and women (red) without diabetes. Vertical error bars indicate the 95% CIs of the mean FIS indices; horizontal error bars indicate the SDs of the obesity indices. The shadowed areas represent the 95% CI of the fit. The bivariate (obesity index, sex and interaction) analysis is presented as an insert in each plot, while the results of multivariate analysis are presented in the tables

Mechanisms through which overweight and obesity increase FIS As insulin secretion is almost exclusively controlled by plasma glucose and by the ability of the beta cell to respond to glucose, we analysed the relationship between obesity and both FPG and fasting beta cell function cross-sectionally and also in prospective data.

As shown in Fig. 2, progressively higher BMI values were associated with a biphasic response of FPG, rising linearly until 26 kg/m^2 and then reaching a plateau. The relationship between FPG and fat% differed between men and women, with women displaying a steeper curve (fat% × sex interaction, p<0.0001) and an increase in FPG across the entire range of fat% values, with no indication of a plateau. The impact of body fat distribution, as estimated by WHR, on FPG did not differ between men and women, despite the expected different range of values. In multivariate analysis (Fig. 2), among the primary obesity indices only waist circumference was an independent predictor of FPG, coming below age and sex, which were the strongest predictors (r^2=0.17).

To assess beta cell function in the fasting condition, we analysed insulin secretion at a plasma glucose concentration of 5 mmol/l (ISR@5, expressed in U/h), derived from OGTT beta cell modelling. This measure represents the beta cell's ability to respond to a fixed plasma glucose level (5.0 mmol/l), allowing for comparison between participants with different fasting values. ISR@5 proved highly sensitive to BMI and fat%, especially in men (Fig. 2). In women, the dose–response curve was less steep, with a clear rise only evident above 35% fat or a BMI of 30 kg/m^2. In multivariate analysis over the primary variables, age had the strongest (negative) impact on ISR@5, followed in order of relevance by fat mass (positive) and the interaction fat mass × male sex, although they explained only a small fraction of ISR@5 variability (r^2=0.11).

Among the 1016 individuals that completed the 3.5 years of follow-up, 390 participants gained more than 2 kg from baseline (Δ weight=+5.1 ± 3.8 kg, Δ fat mass=+3.4 ± 3.9 kg, Δ fat%=+2.7 ± 3.8%), 427 participants lost more than 2 kg (Δ weight=−4.7 ± 2.8 kg, Δ fat mass=−2.6 ± 4.3 kg, Δ fat%=−2.0 ± 5.4%) and the weight of 202 remained stable (Δ weight=0 ± 1 kg, Δ fat mass=+0.4 ± 2.6 kg, Δ fat%=+0.7 ± 3.9%). The proportion of women and men was similar in the three groups. At baseline, FIS was similar in the three groups and, as expected, it increased in weight gainers, did not change in those who were weight stable and decreased in weight losers. Notably, these changes closely mirrored those predicted by the cross-sectional analysis



FPG (mmol/l), r^2=0.17

Variable	Stβ	p
Age	0.19	<0.0001
Male sex	0.22	0.0007
Waist	0.16	0.0032
Fat mass	0.10	0.066
Height	0.07	0.113
Male sex × fat mass	-0.04	0.126
FFM	-0.07	0.359
Hip	-0.02	0.643

ISR@5 (U/h), r^2=0.11

Variable	Stβ	p
Age	-0.18	<0.0001
Fat mass	0.27	<0.0001
Male sex × fat mass	0.12	<0.0001
Height	-0.12	0.0127
FFM	0.12	0.157
Waist	0.04	0.516
Hip	0.01	0.893
Male sex	0.01	0.911

Fig. 2 Polynomial third-order fit of the mean data of FPG (**a**, **b**) and ISR@5 (**c**, **d**) across sex-specific deciles of two different obesity indices (BMI and fat%) in men (blue) and women (red) without diabetes. Vertical error bars indicate the 95% CIs of the mean of the variables on the *y*-axis, and horizontal bars indicate the SDs of the obesity indices. The shadowed areas represent the 95% CI of the fit. The bivariate (obesity index, sex and interaction) analysis is presented as an insert in each plot, while the results of multivariate analysis are presented in the tables

conducted on baseline data (Fig. 3). FPG increased in all the three groups but its rise was greater in those who gained weight (+0.20 ± 0.63 mmol/l) than in those who remained weight stable (+0.11 ± 0.55 mmol/l, $p<0.03$) or lost weight (+0.06 ± 0.55 mmol/l, $p<0.006$) (Fig. 3). ISR@5 declined in both weight losers and those with stable weight (−0.17 ± 1.9 and −0.16 ± 1.0 U/h, respectively; $p<0.002$ for both) but not in weight gainers (−0.06 ± 1.1 U/h). Interestingly, with respect to cross-sectional data, the decrease of ISR@5 in those with stable weight was greater while the increase in weight losers was smaller than expected (Fig. 3). Across the entire dataset, the change in FIS (expressed in U/h) was positively correlated with the change in fasting glucose (Stβ +0.23) and negatively correlated with the change in ISR@5 (Stβ −0.16).

Aetiology of obesity-induced insulin hypersecretion In search of factors that might explain the link between overweight/obesity and insulin hypersecretion, we built a multivariate model with the metabolic variables that are affected by the degree of adiposity and also have the potential to directly modulate insulin secretion, namely insulin sensitivity, plasma leptin and NEFA, along with height, waist circumference, fat mass (kg), sex and the interaction between sex and fat mass. As shown in Table 1, all these variables contributed to explaining the inter-individual variability of FIS but, compared with the model with only anthropometric variables, the increase in r^2 was modest (changed from 0.43 to 0.49). The impact of fat mass, though reduced with respect to the model without metabolic variables (Stβ changed from 0.56 to 0.27), remained statistically significant and substantial, ranking among the highest. Interestingly, plasma leptin ranked second in terms of strength of the association, followed by insulin sensitivity. This pattern of association was not modified by adding family history of diabetes (present in 27% of participants, Stβ −0.04) or IGT (Stβ 0.09) into the model. We also verified whether the fat-related metabolic variables could explain the association between obesity and the major direct mechanisms that sustain insulin secretion, plasma glucose or ISR@5. Age was the strongest

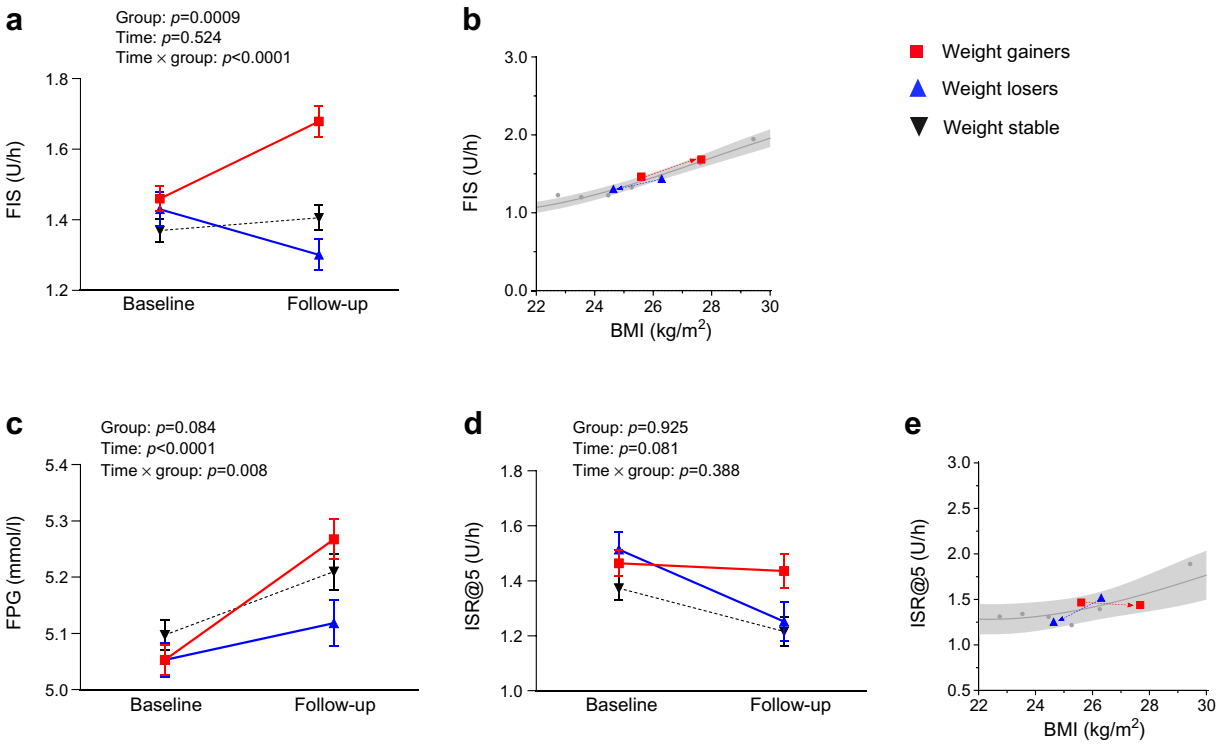


Fig. 3 (**a**, **c**, **d**) Mean values and SEM of non-normalised FIS (**a**), FPG (**c**) and ISR@5 (**d**) at baseline and at 3.5 years of follow-up in the participants from the follow-up cohort (n=1016) who gained (≥2.0 kg; red line), maintained (dotted black line) or lost (≤−2.0 kg; blue line) weight relative to baseline. (**b**, **e**) The FIS (**b**) and ISR@5 (**e**) data at baseline and follow-up were plotted vs BMI together with the curves based on cross-sectional data (grey lines) and their 95% CI (grey area)

Table 1 Multivariate analysis of anthropometric and metabolic variables affecting fasting whole-body FIS, plasma glucose and ISR@5

Variable	FIS			FPG			ISR@5		
	Stβ	LogW	Rank	Stβ	LogW	Rank	Stβ	LogW	Rank
Age	NS	NS	-	0.19	11.2	1	−0.16	7.7	3
Male sex	0.22	5.3	6	0.17	2.9	3	NS	NS	-
Fat mass (kg)	0.27	9.7	4	0.17	4.3	2	NS	NS	
Fat mass × male sex	0.18	13.7	1	NS	NS	-	0.18	8.9	2
Waist (cm)	0.21	6.9	5	NS	NS	-	NS	NS	-
Height (cm)	NS	NS	-	NS	NS	-	NS	NS	-
M/I (μmol^{-1} min^{-1} kg_{ffm}^{-1} nmol^{-1} l)	−0.17	11.4	3	NS	NS	-	−0.16	7.1	4
NEFA (mEq/l)	−0.09	4.4	7	NS	NS	-	NS	NS	-
Leptin (ng/ml)	0.26	11.7	2	NS	NS	-	0.30	10.2	1
r^2	0.49			0.18			0.17		

M/I, Insulin sensitivity index from the euglycaemic–hyperinsulinaemic clamp

determinant of FPG, followed by fat mass and male sex and leptin (Table 1). ISR@5 bore strong and independent associations with leptin (positive), fat mass × male sex (positive), age (negative) and insulin sensitivity (negative) (Table 1). To further account for possible heterogeneity introduced by altered glucose tolerance, we performed a sensitivity analysis excluding individuals with IGT. The results of this subgroup analysis (ESM Table 2) were highly consistent with the findings in the whole cohort, confirming fat mass × male sex, fat mass, waist circumference, leptin and insulin sensitivity as the strongest independent determinants of FIS. We further repeated the analysis including ALT, which increased progressively across BMI deciles (ESM Table 1), as a surrogate marker of possible subclinical fatty liver disease (ESM

Table 3). The results were unchanged, with fat mass × male sex, fat mass, waist circumference, leptin and insulin sensitivity remaining the main predictors of FIS, while ALT was not a significant contributor.

Glucose production and obesity-induced insulin hypersecretion Considering that beta cell activity is finely regulated to achieve a sinusoidal insulin concentration that regulates hepatic glucose production in response to the two major positive stimuli (i.e. glucagon and NEFA), we analysed these data. Although EGP was only measured in a subset (n=368) of the whole cohort, the relationship between FIS and fat mass in men and women was consistent with that observed in the full cohort (ESM Fig. 3). The analysis was performed over sex-specific quintiles of fat mass, pooling men and women together to increase the sample size (and the accuracy of the mean estimates); we also used the EGP values normalised per kg of FFM on the basis of our previous evidence that lean body mass is its major determinant [22]. As shown in Fig. 4, whole-body EGP (Fig. 4a), glucagon (Fig. 4c) and NEFA (Fig. 4d) did not change across deciles of fat mass, while FIS showed a progressive linear increase (Fig. 4b). When EGP was plotted against estimated sinusoidal insulin concentration (Fig. 4e), we observed a flat dose–response curve, indicating the presence of either severe hepatic insulin resistance or a fully operating homeostatic system that counteracts an increased EGP. In this cohort, we had no evidence of reduced insulin sensitivity of the liver as estimated through the per cent of clamp-induced EGP suppression, which was independent of both BMI and fat mass, (p=0.699 and p=0.130, respectively).

To look deeper into this issue, we examined the linear fit of EGP vs log-transformed estimated sinusoidal insulin levels, both fasting and during the clamp (Fig. 5) across quintiles of fat mass. The curves displayed similar slopes, indicating a preserved EGP response to the clamp-induced insulin gradient. In each participant, the individual slope and the intercept were calculated. The mean of individual values across quintiles of fat mass are presented in Fig. 5 along with the predicted EGP at a fixed fasting sinusoidal insulin concentration (EGP@SI86) corresponding to the first quartile mean value (86 pmol/l). While no statistically significant difference was present in the slopes, both the intercepts and EGP at fixed insulin increased across fat mass quartiles

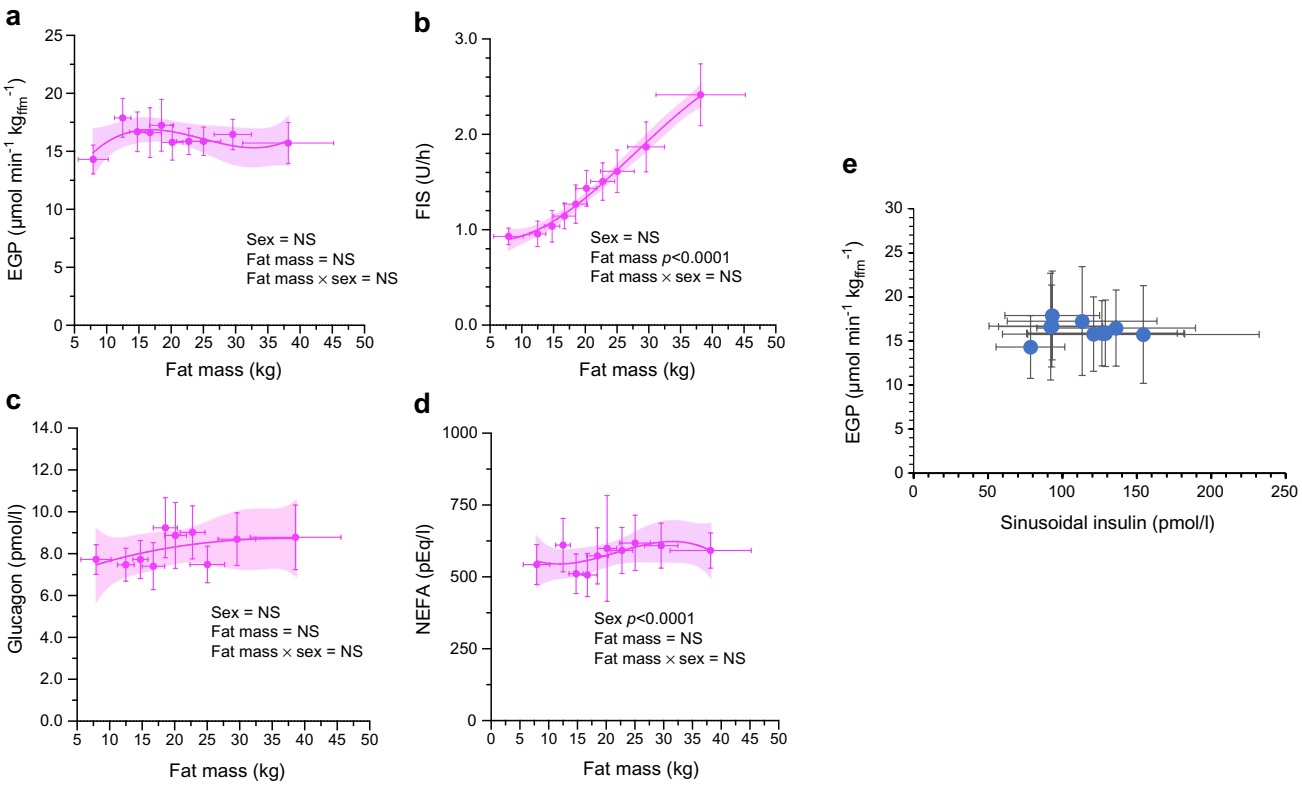


Fig. 4 (**a**–**d**) Polynomial third-order fit of the mean data of EGP (**a**), FIS (**b**), plasma glucagon (**c**) and NEFA concentrations (**d**) across BMI deciles in the subset of men and women with EGP data (n=368). Vertical error bars indicate the 95% CIs of the mean of the variables on the y-axis, and horizontal bars indicate the SDs of the obesity indices. The shadowed areas represent the 95% CI of the fit. The bivariate (fat mass, sex and interaction) analysis is presented as an insert in each plot. (**e**) EGP (mean and SD) is plotted vs estimated fasting sinusoidal insulin concentration (mean and SD)

suggesting the presence of a primary EGP increase with a preserved response to insulin.

Discussion

In the EGIR-RISC cohort, the deciles of BMI simulate the longitudinal progression from low-normal weight to overweight and obesity, with a continuous increase in body weight (against a constant height), associated with a continuous increase in fat mass (up to fourfold) and a modest increase in FFM (up to 20%), and also associated with the gradual emergence of insulin resistance and of all the features of the metabolic syndrome. Notably, the potential confounding effect of ageing was attenuated due to the relatively homogeneous age across deciles. Furthermore, the inclusion of participants selected for the absence of morbid obesity, diabetes, hypertension and dyslipidaemia (and their treatments) avoided the usual confounders seen in the literature in the evaluation of the direct consequences of body size expansion on the major physiological determinants of insulin secretion and glucose homeostasis.

A key finding of our study is that the effect of overweight/obesity on FIS is continuous, with no clear threshold, and appears to be mostly driven by fat mass and waist circumference (Fig. 6). Additionally, we found that the effect of obesity (BMI) on insulin secretion is somewhat underestimated when normalised for BSA. This effect is quantitatively relevant and more pronounced in men, in whom FIS appears to be more sensitive to expansion of fat depots. The features of obesity with the greatest influence on FIS are total fat mass (in kg) and waist circumference, which, probably, simultaneously capture both the metabolic and the body size expansion phenomena. The expansion of body mass per se, although frequently overlooked, contributes to a significant extent to insulin hypersecretion. Multivariate analysis including sex, age, WHR and fat% suggests that any increase of 1 BMI unit imposes a clinically significant increase in basal insulin needs (+1.6 ± 0.2 U/24 h) in addition to the independent contributions of increases in fat% (+0.5 ± 0.1 U/24 h per unit) and WHR (1.4 ± 0.5 U/24 h per 0.1 U). The reduced sensitivity of women to the effects of fat mass expansion is only partially explained by the difference in body fat distribution (as captured by WHR) and thus is likely to be related

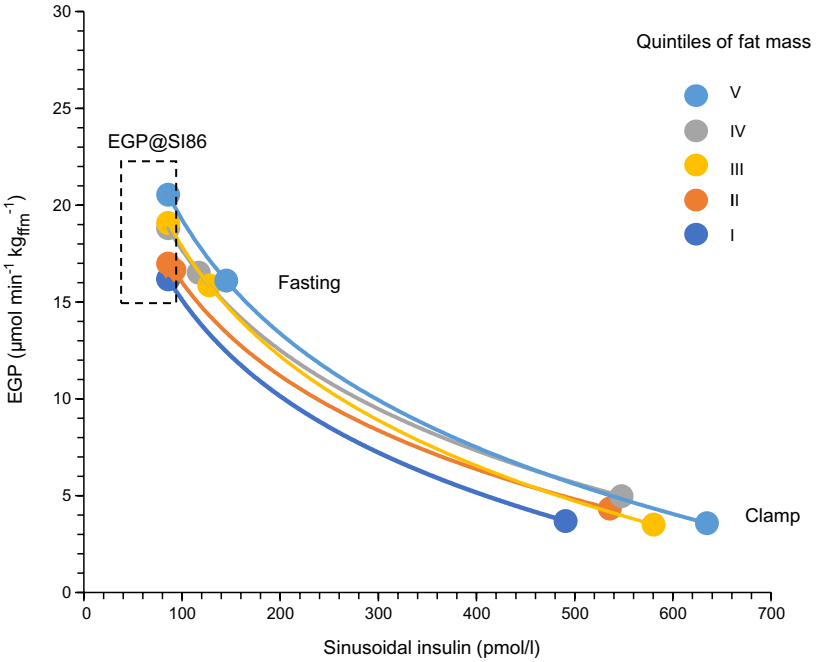


Fig. 5 Plot of EGP vs the estimated sinusoidal insulin concentration both in fasting conditions and during the last 20 min of the euglycaemic insulin clamp in men and women grouped in sex-specific quintiles of fat mass. The data points marked by the dashed rectangle represent predicted log fit values of EGP for the sinusoidal insulin concentration corresponding to the first quartile value (86 pmol/l; EGP@SI86). Mean ± SEM values of fat mass and the data generated by the individual regression analysis per fat mass quartiles are indicated in the table

ANOVA for quintiles of fat mass (I-V)						
Variable	**I**	**II**	**III**	**IV**	**V**	***p***
Fat mass	10±3	16±2	19±2	24±3	34±7	<0.001
Slope	-7.3±4.1	-7.3±6.4	-7.6±4.8	-8.4±4.4	-8.9±4.8	0.208
Intercept	48.8±22.0	47.8±28.0	52.3±26.3	56.2±23.5	60.0±29.2	0.028
EGP@SI86	16.2±5.6	16.7±5.2	18.5±6.3	18.8±5.5	20.4±8.4	<0.001

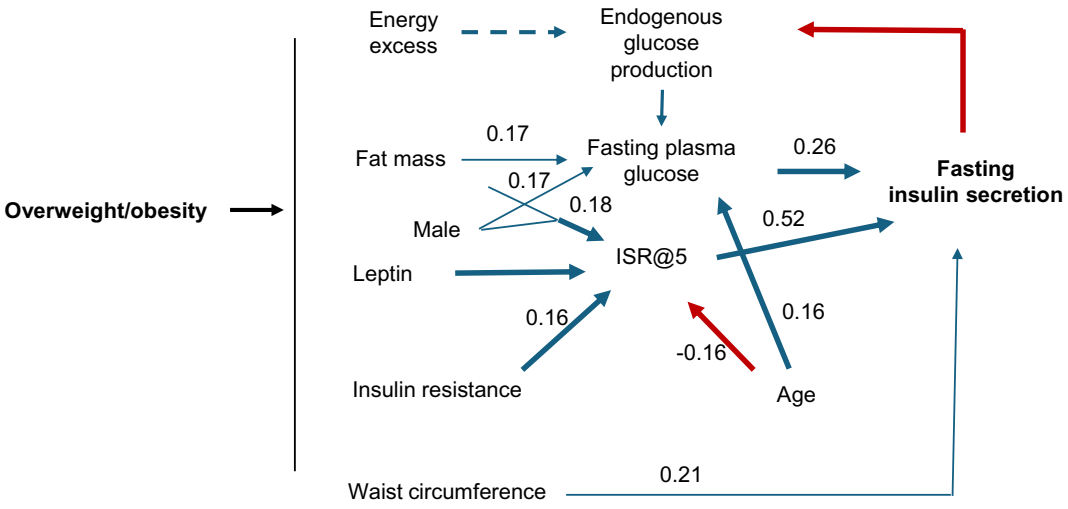


Fig. 6 Depiction of the hypothesised mechanisms through which obesity produces an increase in FIS. Stimulatory effects are represented by blue arrows and inhibitory effects by red arrows; the values represent the strength of the association in a multivariate model (Stβ). The dashed line indicates effects that are not proven by our analysis but are plausible and consistent with the literature

to the different biology of fat cells in women [23]. As obesity is also associated with liver involvement, we examined ALT and AST across BMI deciles. ALT, but not AST, increased with BMI, reflecting the greater liver specificity of ALT and its sensitivity to steatosis [24]. When ALT was added to the multivariate model (ESM Table 3), it was not a significant determinant of FIS and the hierarchy of predictors was unchanged, indicating that subclinical fatty liver is unlikely to explain the associations observed. The obesity-related increase in beta cell workload is sustained by hyperglycaemia in the normal weight range, then by an upshift of ISR@5 in the overweight/obesity range (Fig. 2) (i.e. an upward shift of the entire insulin secretion–glucose concentration dose–response curve). This represents the main beta cell compensatory mechanism against progression to hyperglycaemia, as it limits the impact of obesity on fasting glucose by enabling beta cells to produce more insulin for the same glucose concentration. Indeed, in the present analysis the impact of BMI on fasting glucose became greater (Stβ from 0.20 to 0.33) when the model was also adjusted for ISR@5, which had a strong independent negative effect (Stβ −0.53). The concept that the increase in ISR@5 protects against obesity-driven fasting hyperglycaemia is also evident when comparing data from men and women. In women, the increase in ISR@5 is both delayed (occurring above a BMI of 26 kg/m^2) and lower, correlating with a more pronounced rise in FPG. Women therefore appear to have a less efficient beta cell compensation in response to obesity. This difference may reflect an underlying difference in beta cell adaptation to obesity in keeping with autopsy studies, which suggest the increase in beta cell mass is less marked in obese women than in obese men [13]. Additionally, the multivariate analysis of the primary variables confirms that ISR@5 is increased by male sex, both per se and in interaction with fat mass and, interestingly, it is also reduced with ageing.

Our longitudinal data corroborate the findings of the cross-sectional analysis regarding the link between overweight and insulin secretion (Fig. 3), although with respect to the mechanisms they suggest a minor role of ISR@5. We interpret this as reflecting a decline in ISR@5 with age, which partially counteracts the increase associated with obesity. Indeed, in the cross-sectional analysis, after adjusting for sex and obesity indices, ISR@5 was negatively associated with age and the multivariate analysis of follow-up data confirms that the increase (or absence of time-related drop) in ISR@5 is the main beta cell compensatory mechanism protecting against hyperglycaemia. Furthermore, the baseline BMI of both body weight gainers and losers, by chance, fell on the flat portion of the BMI vs ISR@5 curve, and the BMI changes were relatively small. The age-dependent decline in ISR@5 possibly justifies the increase in development of hyperglycaemia with ageing [25].

The contribution of the metabolic consequences of fat tissue expansion, such as insulin resistance and the release of adipokines and metabolic substrates, on FIS and its major drivers (plasma glucose and ISR@5), as explored by multivariate analysis (Table 1), suggests that a portion of the effect of fat mass (approximately 50%) was indeed mediated by these factors. Among them, leptin appeared to be the strongest, in agreement with data in rat islets exposed to physiological leptin concentrations [26]. Of interest, in our database plasma leptin concentration was correlated with ISR@5 more strongly in men (r^2=0.18, p<0.0001) than in

women (r^2=0.08, p<0.0001), suggesting a possible role of leptin in the crosstalk between fat and the beta cell and in the sex-related differences. Insulin sensitivity contributes to explaining, although not completely, the effect of fat mass on FIS, and our observation that it also bears a negative relationship with ISR@5 suggests that insulin resistance (possibly by promoting chronic relative feeding-related hyperglycaemia [21]) could be a driver for this beta cell adaptation.

Another key observation is related to the liver. The relationship between EGP and sinusoidal insulin was characterised by a rightward shift as fat mass increased from the lowest to the highest quintile (Fig. 5), suggesting a largely preserved ability of insulin to suppress EGP coupled to an enhanced glucose production at any insulin level. Of note, most of the studies claiming the presence of liver insulin resistance in obesity based their conclusions on a single fasting determination (e.g. [27] and the few studies adopting multiple systemic insulin infusions (e.g. [11]) observed that insulin resistance is limited to insulin concentrations that are far below those attained in the portal circulation or are absent [10]. Moreover, in individuals with obesity, and even in those with obesity and type 2 diabetes, it has been shown that a small gradient in sinusoidal insulin with respect to baseline values can significantly reduce EGP [28]. The reason for this primary liver overproduction of glucose in individuals with obesity cannot be ascertained from our data but there is evidence that it might be explained by energy excess. One week after bariatric surgery EGP in individuals without diabetes remained stable (per kg of body weight) while fasting insulin declined by 50% [29]. In healthy individuals, 5 days of a hyperenergetic (hypercaloric; +50%) balanced diet was able to induce a modest (26%) rise in EGP despite a rise in both plasma C-peptide (+30%) and glucose (+0.46 mmol/l) [30]. Data in individuals with type 2 diabetes also support this hypothesis, as fasting hyperglycaemia (a proxy of enhanced EGP) appears to be extremely sensitive to energy balance: in fact, it is reduced promptly by energy restriction in individuals with obesity and newly diagnosed type 2 diabetes before a significant body weight loss occurs [31]. Additionally, a modest weight loss in overweight individuals with type 2 diabetes is associated with a significant reduction in plasma glucose and insulin, with no change in EGP [12]. Moreover, EGP and fasting insulin in overweight individuals with type 2 diabetes have been shown to fall after 1 week of hypoenergetic diet [32]. In a more extreme scenario, using a rat model with type 2 diabetes with fasting glucose levels around 13.3 mmol/l, even a 3-day period of energy restriction significantly reduced fasting glucose (by 4.2 mmol/l), plasma insulin levels (by 50%) but only reduced EGP by 20% [33]. It can be speculated that the primary cause of glucose overproduction in obesity is a chronic greater availability of energy and carbon moieties, as elegantly shown in experimental studies [33]. The increased EGP is expected to transiently increase plasma glucose until the beta cells release the amount of insulin necessary to restore EGP to normal levels. The size of this glucose gradient can be very small since it is inversely proportional to the individual beta cell function, which in a substantial fraction of normal individuals is high. This might justify why plasma glucose is unable to explain a larger fraction of FIS variability.

Clinical implications The knowledge of the details of the physiological relationship between obesity and glucose homeostasis is crucial in the design of more effective therapeutic and preventive strategies for type 2 diabetes. The evidence that the detrimental effect of fat mass on fasting glucose homeostasis is attenuated in women implies that, compared with men, they are expected not only to be less vulnerable to obesity-induced diabetes but also to benefit less from the same weight reduction strategy. We are not aware of any previous study directly addressing this hypothesis with relevant clinical implications. The evidence that the association of BMI with FIS is continuous across the low-normal weight and class I obesity range and that plasma glucose is involved in supporting this additional insulin secretion has clinical implications. Our finding that the association between BMI and FIS is continuous across the low-normal weight to class I obesity range, and that plasma glucose contributes to sustaining this additional insulin secretion, carries important consequences. First, it aligns with epidemiological data showing that the relationship between BMI and diabetes risk is linear starting from a BMI of 20 kg/m^2 [34]. Second, it predicts that weight loss is likely to reduce endogenous insulin requirements and therefore lower FPG, even in individuals with normal body weight, particularly when beta cell function is impaired (because the reduced slope of the glucose–insulin secretion dose–response curve amplifies the effect), as occurs in people with type 2 diabetes. Indeed, weight loss has recently been shown to induce diabetes remission even in individuals with a BMI below 27 kg/m^2 [35]. In addition, our data suggests the presence in individuals with overweight/obesity of an enhanced hepatic glucose production that is not a consequence of a reduced liver insulin sensitivity, possibly representing a novel cause of hyperinsulinaemia and hyperglycaemia. Provided that energy restriction per se exerts a lowering effect on EGP, the marked and fast improvement in FPG, observed before body weight changes, in individuals with type 2 diabetes becomes fully explained and justified as an effective treatment strategy.

Limitations Our findings, based primarily on cross-sectional data and confirmed over a relatively short follow-up period, need to be replicated in longitudinal studies of greater duration. Body fat distribution, from our data, appears to play a secondary role with respect to total fat mass in stimulating insulin secretion. However, we must acknowledge that WHR

is a crude index of visceral fat accrual and therefore we cannot exclude that a more accurate measure of intra-abdominal fat and/or liver fat [27, 36] might have a stronger relationship with FIS than WHR. We also acknowledge that our findings related to hepatic glucose overproduction are largely inferential and the data did not allow us to quantify its contribution to insulin hypersecretion. However, it should be noted that its demonstration would require a complex experimental setting (i.e. fasting EGP measured at identical fasting sinusoidal insulin concentrations) that is unfeasible in large-scale studies. Although we excluded participants with known liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), which could impact glucose homeostasis, was not specifically assessed in this cohort. However, additional analyses including liver enzymes as surrogate markers did not significantly change our findings. Another limitation is the lack of data on HbA_{1c}; however, as no participants had diabetes and glucose metabolism was extensively assessed, the absence of HbA_{1c} is unlikely to affect our conclusions. Provided that our cohort is of relatively healthy individuals, we cannot generalise our findings to the real world, where fasting hyperinsulinaemia and obesity are likely to be modulated by other mechanisms such as inflammation [37], stress-hormones [38] and the autonomic nervous system [39].

Conclusions In synthesis, the absolute expansion of body fat stores produces a linear increase in FIS that is more accentuated in men than in women and is driven by hyperglycaemia and an upregulation of beta cell insulin secretion (as measured by ISR@5). This effect is only partially explained by body fat distribution, peripheral insulin resistance, leptin or NEFA and is not associated with a reduced liver response to insulin. Age, by negatively affecting the uprise of beta cell function, which appears to be promoted by insulin resistance and leptin, amplifies the reliance of the response on hyperglycaemia. The analysis of the EGP response to insulin suggests that body fat store expansion is associated also with an upward shift of the relationship between EGP and sinusoidal insulin, which is likely to depend on energy balance and could be responsible for a substantial fraction of FIS, not explained by the anthropometric, hormonal and plasma substrate consequences of overweight/obesity.

Supplementary Information The online version of this article (https://doi.org/10.1007/s00125-025-06643-9) contains peer-reviewed but unedited supplementary material.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Contribution statement AN and AM conceptualised the study. AN, MC and DT analysed the data and wrote the manuscript. JP, RG, AG, JN, NL, GM contributed to the interpretation of the data and revised the manuscript. AM performed the glucose tracer and beta cell function modelling. All authors commented on and approved the final version of the manuscript. MC and AN are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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