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Evaluation of common genetic variants identified by GWAS for early onset and morbid obesity in population-based samples

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Abstract

Background—Meta-analysis of case-control genome wide association studies (GWAS) for early onset and morbid obesity identified four variants in/near the *PRL*, *PTER*, *MAF* and *NPC1* genes.

Objective—We aimed to validate association of these variants with obesity-related traits in population-based samples.

Design—Genotypes and anthropometric traits were available in up to 31 083 adults from the Fenland, EPIC-Norfolk, Whitehall II, Ely and Hertfordshire studies and in 2 042 children and adolescents from the European Youth Heart Study. In each study, we tested associations of rs4712652 (near-*PRL*), rs10508503 (near-*PTER*), rs1424233 (near-*MAF*) and rs1805081 (*NPC1*), or proxy variants ($r^2 > 0.8$), with the odds of being overweight and obese, as well as with BMI, percentage body fat (%BF) and waist circumference (WC). Associations were adjusted for sex, age and age² in adults and for sex, age, age-group, country and maturity in children and adolescents. Summary statistics were combined using fixed effects meta-analysis methods.

Results—We had 80% power to detect ORs of 1.046 to 1.092 for overweight and 1.067 to 1.136 for obesity. Variants near *PRL*, *PTER* and *MAF* were not associated with the odds of being overweight or obese, or with BMI, %BF or WC after meta-analysis ($P > 0.15$). The *NPC1* variant rs1805081 showed some evidence of association with %BF (beta=0.013 SD/allele, $P=0.040$), but not with any of the remaining obesity-related traits ($P > 0.3$).

Conclusion—Overall, these variants, which were identified in a GWAS for early onset and morbid obesity, do not seem to influence obesity-related traits in the general population.

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Supplementary information is available at The International Journal of Obesity's website.

Keywords

Obesity-susceptibility loci; genome-wide association; morbid; early-onset; anthropometric traits; children and adolescents; population-based

Introduction

Meta-analyses of genome-wide association studies (GWAS) for continuous obesity-related traits have so far identified 32 loci for BMI and 14 loci for waist-hip ratio^{1,2}. Meyre et al³ previously hypothesized that children with early-onset obesity (before the age of six yrs) and adults with morbid obesity (BMI ≥ 40 kg/m²) may be enriched for genetic variants that contribute to obesity in the general population. After a two-stage meta-analysis of case-control GWAS, including 3 447 obese cases and 3 827 normal weight controls, four variants in or near previously unanticipated genetic regions showed association with the risk of early onset and morbid obesity. These variants were located near *PRL* (Chr 6), near *PTER* (Chr 10), near *MAF* (Chr 16) and in *NPC1* (Chr 18). Subsequent follow-up of these hits in two population-based samples of 5 291 children and 4 417 adults showed limited evidence of association with BMI, with each additional obesity risk-allele increasing BMI by 0.001 to 0.091 kg/m² in children and by 0.017 to 0.04 kg/m² in adults³. *P*-values for association with BMI ranged from 3.2×10^{-6} to 0.98 in children and from 4.6×10^{-2} to 0.61 in adults³. Hence, in spite of associations with early onset and morbid obesity in case-control studies, the relevance of these variants for obesity and adiposity variation in the general population remains inconclusive.

In the present study, we examined whether the four loci identified in GWAS for early onset and morbid obesity also contribute to obesity-susceptibility and adiposity variation in the general population. To ensure sufficient power to find associations, we meta-analysed summary statistics in up to 31 083 adults from the Fenland, EPIC-Norfolk, Whitehall II, Ely and Hertfordshire studies and in 2 042 children and adolescents from the European Youth Heart Study (EYHS) (Tables 1-2; Supplementary Table 1).

Materials and Methods

Study population and anthropometry

Genetic information and data on anthropometric traits were available in up to 31 083 adults from the Fenland, EPIC-Norfolk, Whitehall II, Ely and Hertfordshire studies, as well as in 1 252 children and 790 adolescents from the EYHS (Tables 1-2). Detailed information about study designs, participant recruitment and phenotype collection has been described elsewhere⁴⁻¹².

Body mass and height were measured using standard procedures with participants dressed in light clothing and barefoot¹³. Overweight and obesity were defined as BMI ≥ 25 and ≥ 30 kg/m² in adults and using age- and sex-specific thresholds of BMI in the EYHS ($\geq 90^{\text{th}}$ percentile for overweight; $\geq 99^{\text{th}}$ percentile for obesity)¹⁴. Normal weight was defined as BMI < 25 kg/m² in adults and a BMI $< 90^{\text{th}}$ percentile in the EYHS.

Waist circumference (WC) was measured midway between the lower rib margin and the iliac crest using a non-stretchable tape measure in all studies^{5, 6, 8, 9, 12, 15}. We applied several techniques to determine percentage body fat (%BF). Dual energy X-ray absorptiometry (DEXA) (Lunar Prodigy Advanced fan beam scanner; GE Healthcare, Bedford, UK) was used in a subsample of the Fenland study (subsample 1, $n = 1\,870$)^{9, 15}, whereas we used bio-impedance in a second, independent subsample of the Fenland study

(subsample 2, $n = 3\,184$) (Tanita BD-418AM, Tanita Europe GmbH, Sindelfingen, Germany)⁹, as well as in the Whitehall II (Tanita TBF-300; Tanita Europe GmbH, Sindelfingen, Germany), Ely (Bodystat 1500; Bodystat, Isle of Man, UK)⁶ and EPIC-Norfolk (Tanita 531; Tanita Europe GmbH, Sindelfingen, Germany) studies. In data from 2 535 Fenland participants, %BF as assessed using bio-impedance and DEXA were strongly correlated ($r=0.92$)¹⁶. In the Hertfordshire study, %BF was derived from the sum of four skinfolds (triceps brachial, biceps brachial, sub-scapular and supra-iliacal sites in mm) using the method of Durnin and Wormsley¹⁷. Maturity specific equations (pre-pubertal and pubertal)¹⁸ were used to derive %BF from the sum of two skinfolds in the EYHS (triceps brachial and sub-scapular sites in mm)¹⁹. All techniques used explain 80%-90% of the variance in body composition as assessed using the four-compartment model^{18, 20-22}. Sexual maturity was assessed in the EYHS using the five-stage Tanner scale for breast development in girls and pubic hair in boys²³.

Each study was approved by the local scientific committees and was performed in accordance with the declaration of Helsinki. All adults gave their written informed consent. In the EYHS, parents gave written informed consent for their child to participate and all children and adolescents gave verbal consent.

Genotyping

In subsample 1 of the Fenland study, as well as in the EYHS and Hertfordshire studies, we genotyped rs4712652 near *PRL*, rs10508503 near *PTER*, rs1424233 near *MAF* and rs1805081 in *NPC1*. The latter three were genotyped using a Sequenom iPLEX® platform (Sequenom, San Diego, Ca, USA)²⁴, whereas rs4712652 was genotyped using Custom TaqMan® SNP Genotyping Assays, according to the manufacturer's protocol (Applied Biosystems, Warrington, UK). Taqman assays were also used to genotype rs4712652, rs10508503, rs10514465 (a proxy for rs1424233 ($r^2 = 1.000$; $D' = 1.000$)) and rs1805081 in the EPIC-Norfolk study.

In the Ely and Whitehall II studies, as well as in subsample 2 of the Fenland study, genotype information was available from the metabochip; a custom iSELECT array containing ~195k SNPs that was designed to support large-scale follow-up of putative associations with metabolic and cardiovascular traits. The metabochip contains genetic information for rs6901423 (a proxy for rs4712652 ($r^2 = 0.803$; $D' = 0.927$)), rs8048408 (a proxy for rs1424233 ($r^2 = 0.967$; $D' = 1.000$)) and rs1805081.

All markers passed quality control criteria; call rates > 95%, P -value for Hardy-Weinberg equilibrium > 0.0125 (Bonferroni correction for four independent tests at $\alpha = 0.05$), as determined by a χ^2 test with one degree of freedom. An exception was rs4712652 in the EPIC-Norfolk, Whitehall II and Hertfordshire studies ($P < 0.0125$) (Supplementary Table 1). For association analyses of rs4712652, we excluded the latter samples from further analyses.

Statistical analysis

Before testing for associations, all traits were transformed to normal distributions with a mean of zero and SD of one in each study separately using inverse normal transformation. Hence, effect sizes can be interpreted as Z-scores, which allow comparison across traits and age-groups.

Logistic regression was used to test the association of each SNP with the odds of being overweight or obese compared with non-overweight individuals ($BMI < 25\text{ kg/m}^2$; control group). A sensitivity analysis showed that using non-obese individuals ($BMI < 30\text{ kg/m}^2$) as the control group did not change the results. We also tested the association of each SNP with BMI, %BF and WC using linear regression. For the near-*PRL* variant (rs4712652),

associations with BMI ($n = 4\,879$) and %BF ($n = 3\,068$) were recently reported in the PPP-Botnia study²⁵, whereas for the near-*PTER* (rs10508503), near-*MAF* (rs1424233) and *NPC1* (rs1805081) variants, associations with BMI and WC were recently described in the Inter99 study ($n = 6\,514$)²⁶. Additional meta-analyses were performed in which the latter results were pooled with those of the current study. To the best of our knowledge, the PPP-Bothnia and Inter99 studies represent the only population-based samples with data from individuals of white European descent in which the association of these SNPs with adiposity-related traits have been described since they were discovered.

All associations were tested assuming an additive model of inheritance. However, based on the results of the discovery study³, we additionally examined associations under alternative models for the near-*PRL* (recessive model) and near-*PTER* (dominant model) variants. Risk-alleles were defined as the obesity-susceptibility increasing alleles in the discovery study³. All associations were adjusted for sex, age and age² in adults, and for sex, age, age-group (children versus adolescents), country and maturity in the EYHS. In all studies, associations with WC were additionally adjusted for height.

In a secondary analysis, we examined interactions of SNPs with sex and age for case-control analyses and continuous traits by adding an interaction term to the model (SNP*sex, SNP*age). Interactions with sex and age were considered significant if $P < 6.25 \times 10^{-3}$ (Bonferroni correction for eight independent tests, i.e. four SNPs and two interactions per SNP, at $\alpha = 0.05$).

Study-specific betas and SEs of the main effect associations and interaction terms were meta-analysed for continuous outcomes using the inverse variance weighted fixed effects method. We used the same method to perform meta-analyses of study specific odds ratios and 95% CIs for the case-control analyses. *P*-values for associations reported in the PPP-Botnia²⁵ and Inter99 studies²⁶ were pooled with those of the current studies using the weighted Z-score approach.

Power calculations were performed to estimate the power of our study to detect the odds ratios for obesity that were observed after meta-analysis of four case-control studies for early onset and morbid obesity in the replication stage of the discovery study³. In addition, we estimated the odds ratio for risk of overweight and obesity that we would be able to identify with 80% power at an α -level of 0.05 given our sample size. Given the relatively small sample of the EYHS, we had insufficient power to conclusively validate associations in children and adolescents. Nevertheless, we choose to provide and cautiously interpret the results as they are the first describing associations between these four loci and obesity-related traits in a population-based sample of children and adolescents. This way, the summary statistics of these associations will be valuable for others to use in future meta-analyses in young individuals. Furthermore, summary statistics from the EYHS were included in the full meta-analysis of our study, thereby further increasing the power to find associations.

We performed statistical analyses using SAS version 9.2 for windows (SAS Institute, Cary, NC, USA). We used STATA software for inverse variance weighted meta-analysis (metan) (STATA version 10.1, StataCorp, College Station, TX), whereas METAL was used for the weighted Z-score meta-analysis²⁷. Power calculations were performed using Quanto (Quanto v1.1.1: <http://hydra.usc.edu/gxe>). Associations presented are for meta-analyses of all new data assuming an additive model unless stated otherwise. A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Power

For the near-*PTER*, near-*MAF* and *NPC1* variants, we had >99% power to detect the ORs observed by Meyre et al for overweight and obesity (Supplementary Table 2). The power was generally lower for the near-*PRL* variant (88% for overweight; 61% for obesity) as the sample size was smaller. With the available sample size, we had 80% power to detect ORs of 1.046 to 1.092 for overweight and 1.067 to 1.136 for common obesity (Supplementary Table 2).

Meta-analysis

None of the risk alleles were associated with increased odds of being overweight or obese after meta-analysis of results from our population-based studies ($P > 0.15$) (Figure 1).

We found no evidence of association between any of the four variants and BMI after meta-analysis ($P > 0.3$) (Figure 2). We subsequently examined associations of the four variants with %BF and WC. Except for an association of the *NPC1* variant (rs1805081) with %BF (beta = 0.013 SD/allele, $P = 0.040$), none of the variants showed association with %BF ($P > 0.3$) or WC ($P > 0.4$) (Figure 2). Heterogeneity in effect sizes was low to moderate for the near-*PRL*, near-*PTER*, near-*MAF* and *NPC1* variants ($I^2 = 0.0\% - 61.9\%$) (Figures 1-2).

Including recently reported associations of the near-*PRL* variant with BMI and %BF²⁵ and of the near-*PTER*, near-*MAF* and *NPC1* variants with BMI and WC²⁶ in the meta-analysis did not change the results (Supplementary Table 3). Furthermore, results remained unchanged after assuming an alternative mode of inheritance for the near-*PRL* (recessive model) and near-*PTER* (dominant model) variants, based on the results of the discovery study (Supplementary Table 4)³. A sex-specific association of the near-*PRL* variant with BMI and %BF was reported in the PPP-Botnia study²⁵. In a secondary analysis, none of the four variants showed evidence for an interaction with sex or age in either case-control analyses (Supplementary Table 5), or for BMI, %BF or WC (Supplementary Table 6) after considering the additional number of tests performed.

Discussion

Based on a meta-analysis of GWAS for early onset and morbid obesity, variants in/near *PRL*, *PTER*, *MAF* and *NPC1* were previously considered relevant for common obesity and BMI variation³. So far, it remains unclear whether these variants are indeed associated with adiposity variation and obesity-susceptibility in the general population, as was confirmed for many of the loci identified in large-scale meta-analyses of GWAS for BMI², waist-to-hip ratio adjusted for BMI¹ and %BF¹⁶. While our study had sufficient power to identify small effects on the risk of overweight and obesity, none of the variants showed consistent and convincing evidence of such associations. These variants were not associated with the odds of being overweight or obese, nor were they associated with BMI, %BF and WC after meta-analysis of data from up to 33 045 population-based samples. Taken together, our findings suggest that the contribution of these variants to adiposity in the general population is likely limited. However, based on our findings, we cannot exclude the possibility that individuals with early onset and morbid obesity are enriched for rare, functional variants in high LD with the variants studied here. We had 62% power to detect the odds ratio for obesity (OR = 1.10) that was observed by Meyre et al for the near-*PRL* variant³. However, in our meta-analyses, ORs were 1.02 for overweight and 1.01 for obesity, suggesting that even with a larger sample and thus more power we were not able to confirm the associations observed in the case/control analyses for early onset and morbid obesity. Adding published results from the PPP-Botnia study²⁵ to the meta-analysis for BMI and %BF did not change the results.

Recently, the near-*PRL* variant was shown to significantly interact with sex for BMI ($P = 0.05$) and %BF ($P = 0.04$) in up to 4 879 adults of the population-based PPP-Botnia study. Associations with BMI (beta = 0.36 kg/m², $P = 0.0047$) and %BF (beta = 0.60%, $P = 0.025$) were restricted to male participants, with no associations observed in women (BMI: beta = 0.004 kg/m², $P = 0.98$; %BF: beta = 0.21%, $P = 0.45$)²⁵. However, in line with results from the discovery study³, our study does not show evidence for a sex-specific association of the near-*PRL* variant with BMI and %BF, with marginally larger effect sizes in women than in men ($P > 0.4$).

The observation that the near-*PTER* and near-*MAF* variants were not associated with any of the obesity-related traits in our study, either with or without inclusion of the recently published Inter99 data²⁶, is consistent with a lack of association of these variants with BMI in adults of the population-based DESIR study ($n = 4\,417$, $P > 0.1$)³, as well as in adults of the Inter99 cohort, in which effect sizes pointed in the opposite direction ($n = 6\,514$, $P > 0.05$). In addition, no evidence for association with BMI was observed recently for the near-*PTER* and near-*MAF* variants after a large-scale meta-analysis of GWAS ($n = 123\,865$) performed by the GIANT consortium ($P = 0.64$ for near-*PTER*; $P = 0.25$ for near-*MAF*)². In another recent meta-analysis of GWAS, these variants did not show evidence of association with %BF either ($n = 26\,034$, $P = 0.31$ for near-*PTER*; $n = 36\,309$, $P = 0.48$ for near-*MAF*)¹⁶. Taken together, these results do not support an association of the near-*PTER* and near-*MAF* variants with obesity-related traits in the general population. Unfortunately, the aforementioned meta-analyses of GWAS for BMI and %BF did not provide results for associations with the near-*PRL* variant^{2, 16}.

Of the four variants, only the near-*MAF* variant was associated with BMI in children of the population-based NFBC86 study ($n = 5\,291$, $P = 3.2 \times 10^{-6}$)³. With BMI and genotype information available in 1 948 children and adolescents, we had only 16% power to validate the association of the near-*MAF* variant with BMI in the EYHS. Still, since the association with all obesity-related traits was either null or in the opposite direction in the EYHS, we cautiously conclude that our results do not support a role for the near-*MAF* variant in the aetiology of early onset obesity in the general population.

Only the association between rs1805081 in *NPC1* and %BF, the most representative measure of overall adiposity that was available in the present study, reached nominal statistical significance, and was directionally consistent with results presented in the discovery study³. Associations with BMI and WC did not reach significance but were directionally consistent, with slightly smaller effect sizes compared with %BF. Each additional copy of the risk allele was associated with a 0.013 SD increase in %BF, corresponding with ~0.07% body fat, without any heterogeneity in effect size between studies. rs1805081, a non-synonymous (His215Arg) variant in exon 6 of *NPC1*, also showed limited evidence of association with BMI ($P = 2.5 \times 10^{-3}$) and %BF ($P = 4.5 \times 10^{-2}$) in recent GWAS meta-analyses^{2, 16}. *NPC1* is functionally important for the regulation of LDL cholesterol trafficking in mammalian cells²⁸ and plays a central role in maintaining cellular, tissue and whole body lipid homeostasis^{29, 30}. Recent human and animal studies highlighted *NPC1* as a candidate gene for (diet-induced) obesity^{31, 32}.

In conclusion, the results of the present study show that with the possible exception of rs1805081 in *NPC1*, variants identified in case-control data sets for early onset and morbid obesity do not seem to have an effect on obesity-related traits in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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to serum triglyceride levels. *Arterioscler Thromb Vasc Biol.* 2010; 30(8):1614–20. [PubMed: 20489167]

Figure 1.

Associations of variants near *PRL* (A), near *PTER* (B), near *MAF* (C) and in *NPC1* (D) with the odds of being overweight and obese compared with non-overweight (control group), calculated using logistic regression in individual studies and after fixed effects meta-analysis of ORs and 95% CI. Associations were adjusted for age, age² and sex in adults and for age, age-group, sex, country and maturity in children and adolescents. Odds ratios (OR) represent the change in outcome for each additional risk allele under an additive model, with risk alleles defined as the obesity-susceptibility increasing alleles in the discovery study.

Figure 2.

Associations of variants near *PRL* (A), near *PTER* (B), near *MAF* (C) and in *NPC1* (D) with BMI, percentage body fat (%BF) and waist circumference (WC), calculated using linear regression in individual studies and after fixed effects meta-analysis of betas and standard errors. Associations were adjusted for age, age² and sex in adults and for age, age-group, sex, country and maturity in children and adolescents. Associations with WC were additionally adjusted for height. As all traits were inverse normally transformed, betas represent the change in outcome for each additional risk allele under an additive model, expressed in SD units/ allele. Risk alleles are defined as the obesity-susceptibility increasing alleles in the discovery study.

Table 1

Descriptive characteristics of children and adolescents of the EYHS stratified by sex

	Children		Adolescents	
	Boys	Girls	Boys	Girls
n	586	655	350	434
Age (years)	9.7 ± 0.4	9.6 ± 0.4	15.5 ± 0.5	15.5 ± 0.5
BMI (kg/m ²)	17.1 ± 2.2	17.1 ± 2.6	20.5 ± 2.5	20.5 ± 2.7
Weight (kg)	33.3 ± 6.0	33.1 ± 6.8	62.5 ± 10.1	56.1 ± 8.2
Height (m)	139.1 ± 6.6	138.7 ± 6.7	174.4 ± 7.6	165.3 ± 6.0
Waist circumference (cm)	59.4 ± 5.5	58.4 ± 6.6	71.3 ± 5.9	66.8 ± 5.8
Percentage body fat (%)	23.4 ± 4.5	28.7 ± 5.5	17.7 ± 3.1	24.8 ± 3.5
Normal weight (n / %)	495 / 84.5	568 / 86.7	312 / 89.1	386 / 88.9
Overweight, non-obese (n / %)	75 / 12.8	73 / 11.1	35 / 10.0	45 / 10.4
Obese (n / %)	16 / 2.7	14 / 2.1	3 / 0.9	3 / 0.7

Data are presented as means ± SD for individuals with data on at least one SNP. Obese: BMI ≥ 99th percentile; Overweight, non-obese: BMI ≥ 90th percentile; Normal weight: BMI < 90th percentile.

Table 2

Descriptive characteristics of adults per cohort stratified by sex

	Fenland 1		Fenland 2		EPIC-Norfolk		Whitehall		Ely		Hertfordshire	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
n	838	1 032	1 486	1 698	10 184	10 480	1 699	535	744	855	1 224	971
Age (years)	44.7 ± 7.3	45.3 ± 7.1	46.9 ± 7.2	46.9 ± 7.0	59.1 ± 9.3	58.6 ± 9.3	60.5 ± 5.8	60.6 ± 5.8	61.5 ± 9.1	60.8 ± 9.2	65.9 ± 2.9	66.6 ± 2.7
BMI (kg/m ²)	27.8 ± 4.0	26.8 ± 5.6	27.0 ± 4.1	26.5 ± 5.5	26.5 ± 3.3	26.2 ± 4.2	26.6 ± 3.6	27.1 ± 5.3	27.4 ± 4.0	27.3 ± 5.4	27.1 ± 3.7	27.5 ± 5.0
Weight (kg)	87.3 ± 14.4	71.9 ± 15.7	85.4 ± 14.1	71.2 ± 15.5	80.3 ± 11.4	67.8 ± 11.7	81.9 ± 12.4	70.9 ± 14.5	83.1 ± 13.3	71.1 ± 14.3	82.4 ± 12.7	71.3 ± 13.7
Height (m)	177.2 ± 6.4	163.8 ± 6.4	1.78 ± 0.07	1.64 ± 0.06	174.0 ± 6.6	161.0 ± 6.2	175.2 ± 6.5	161.6 ± 6.4	174.2 ± 6.7	161.4 ± 6.1	174.2 ± 6.4	160.8 ± 5.9
Waist circumference (cm)	99.0 ± 11.5	87.1 ± 13.0	96.4 ± 11.2	85.2 ± 12.8	95.7 ± 9.7	82.1 ± 10.8	95.1 ± 10.3	86.0 ± 12.9	100.0 ± 10.6	87.6 ± 12.6	100.7 ± 10.5	92.2 ± 12.9
Percentage body fat (%)	24.3 ± 5.4	35.9 ± 7.1	23.7 ± 5.7	35.7 ± 7.2	23.5 ± 6.2*	39.7 ± 9.1*	24.3 ± 5.4	36.3 ± 6.8	26.6 ± 5.2	39.9 ± 6.5	28.7 ± 5.3	39.9 ± 5.0
Normal weight (n / %)	205 / 24.5	469 / 45.5	494 / 33.2	806 / 47.5	3 387 / 33.3	4 684 / 44.7	573 / 33.7	198 / 37.0	210 / 28.2	331 / 38.7	352 / 28.8	320 / 33.0
Overweight, non-obese (n / %)	438 / 52.3	323 / 31.3	695 / 46.8	542 / 31.9	5 466 / 53.7	4 125 / 39.4	850 / 50.0	210 / 39.3	372 / 50.0	322 / 37.7	624 / 51.0	386 / 39.8
Obese (n / %)	184 / 18.2	210 / 17.3	285 / 17.6	311 / 16.0	1 307 / 12.4	1 575 / 13.9	271 / 15.4	109 / 15.4	155 / 18.5	226 / 16.9	244 / 19.1	247 / 22.0
Morbidly obese (n / %)	11 / 5.1	30 / 6.0	12 / 2.4	39 / 4.6	24 / 0.7	96 / 2.0	5 / 0.9	18 / 8.3	7 / 3.2	178 / 16.9	4 / 1.1	18 / 5.3

Data are presented as means ± SD for individuals with data on at least one SNP; Percentage body fat for EPIC-Norfolk is from second health check (first follow-up, four yrs after baseline measurements; n = 6 265 and 6 206 for men and women, respectively)

Obese: BMI 30 kg/m²; Overweight, non-obese: 25 kg/m² BMI < 25 kg/m² In comparison, the most recent National Health Survey for England (2009) indicates that 61.3% of adults had a BMI 25 kg/m² and 23% had a BMI 30 kg/m². In the latter health survey, average WC was 96.4 cm in adult men and 87.4 cm in adult women (<http://www.dh.gov.uk/en/publichealth/obesity>)