**BRIEF REPORT**

**FTO, Type 2 Diabetes, and Weight Gain Throughout Adult Life**

A Meta-Analysis of 41,504 Subjects From the Scandinavian HUNT, MDC, and MPP Studies


**OBJECTIVE—**FTO is the most important polygene identified for obesity. We aimed to investigate whether a variant in FTO affects type 2 diabetes risk entirely through its effect on BMI and how FTO influences BMI across adult life span.

**RESEARCH DESIGN AND METHODS—**Through regression models, we assessed the relationship between the FTO single nucleotide polymorphisms rs9939609, type 2 diabetes, and BMI across adult life in subjects from the Norwegian population-based HUNT study using cross-sectional and longitudinal perspectives. For replication and meta-analysis, we used data from the Malmö Diet and Cancer (MDC) and Malmö Preventive Project (MPP) cohorts, comprising a total sample of 41,504 Scandinavians.

**RESULTS—**The meta-analysis revealed a highly significant association for rs9939609 with both type 2 diabetes (OR 1.13; 95% CI 1.07–1.19) and the risk to develop incident type 2 diabetes (OR 1.16; 95% CI 1.12–1.20). The associations remained also after correction for BMI and other anthropometric measures. Furthermore, we confirmed the strong effect on BMI (0.28 kg/m² per risk allele; P = 2.0 × 10⁻²⁶), with no heterogeneity between different age-groups. We found no differences in change of BMI over time according to rs9939609 risk alleles, neither overall (ΔBMI = 0.0

[−0.05, 0.05]) nor in any individual age stratum, indicating no further weight gain attributable to FTO genotype in adults.

**CONCLUSIONS—**We have identified that a variant in FTO alters type 2 diabetes risk partly independent of its observed effect on BMI. The additional weight gain as a result of the FTO risk variant seems to occur before adulthood, and the BMI difference remains stable thereafter. *Diabetes 60:1637–1644, 2011*

*Genomewide association studies (GWAS) have identified a strong correlation between BMI and FTO single nucleotide polymorphisms (SNPs) (1–4), and the association has been confirmed in multiple populations (reviewed in 5). The FTO risk variants are also associated with obesity-related traits (6–8). However, these effects appear to be secondary to weight increase because the associations are attenuated after adjusting for BMI (2). In contrast, we and others have found that the association with type 2 diabetes may not be completely mediated through BMI, because it remains significant after BMI correction (9). This indicates that the relationship between sequence variation in FTO and type 2 diabetes is not fully mediated through BMI or that BMI in some populations does not reveal accurate estimates of the effect of FTO on adiposity.*

Various studies have investigated the effect of FTO variants on BMI and weight in a longitudinal perspective (10–18) but with diverging results. With access to extensive data from three large Scandinavian populations, through a meta-analysis approach using both cross-sectional and longitudinal data, we aimed to investigate whether the FTO risk allele affects type 2 diabetes risk after correction for BMI and whether it influences weight gain during adult life.

**RESEARCH DESIGN AND METHODS**

**Definition of cohorts.** We studied HUNT2, a subset (aged ≥30) of a Norwegian population-based health survey (Nord-Trøndelag Health Study) (10). Our material comprised 1,740 diabetic individuals (1,543 with type 2 diabetes) and 3,856 population-based control subjects drawn from the same study population. We also had access to data on diabetes status, weight, and height from HUNT1 (1985) for 4,625 of the 5,596 subjects in HUNT2 (1995), i.e., 10-year follow-up. During these 10 years, 1,089 individuals developed type 2 diabetes. Diagnosis of diabetes was self-reported or identified by standard tests if random glucose was >8.0 mmol/L.

*The Malmö Diet and Cancer (MDC) cohort (20) with baseline examinations from 1991 to 1996 consisted of 29,449 individuals. All men born between 1923 and 1945 and all women born between 1923 and 1956 from Malmö were...*
invited. Diabetes diagnosis at baseline was self-reported or diagnosed if fasting plasma glucose was ≥7.0 mmol/L.

In the Malmö Preventive Project (MPP) cohort (21), 33,346 subjects from Malmö participated in a health screening. Men were included from 1974 to 1990, and women were included from 1980 to 1992. Eligible participants (25,000) were invited to a rescreening visit during 2002–2006. Of those invited, 16,061 nondiabetic subjects, 2,063 of whom developed type 2 diabetes during follow-up, were included in the current study. Diabetes diagnosis was taken from patient records or if fasting plasma glucose was ≥7.0 mmol/L. Information on age, height, weight, and smoking status were obtained at the baseline visit.

The characteristics of individuals from the three cohorts are shown in Table 1.

SNP selection, genotyping, and quality control. Because the reported FTO and BMI during 10-year follow-up from ΔBMI works to in sequence variants on type 2 diabetes and B variant showed an association genotype and BMI, we used linear SNPs are in strong to perfect linkage disequilibrium 10 does not mediate type diabetes. In an attempt to capture the complex relationship between FTO, BMI, and type 2 diabetes during the life course, we performed an analysis on incident type 2 diabetes. The results remained similar in the longitudinal perspective.

RESULTS

Relationship among FTO, type 2 diabetes, and obesity-related quantitative traits across life span in HUNT. After correction for age and sex, we observed a strong association with type 2 diabetes for rs9396069 in HUNT2. This association remained significant after correction for BMI (OR 1.19 [95%CI 1.09–1.30]; P = 1.8 × 10^-5). The FTO variant also conferred an increased risk for type 2 diabetes after adjustment for waist circumference and waist-to-hip ratio. These results suggested that rs9396069 has an effect on the risk of type 2 diabetes, an effect that cannot be entirely explained through increased BMI or central obesity.

Using a cross-sectional design, we observed the FTO-associated allele-wise increase in BMI persisted at the same level throughout life (Supplementary Fig. 1). In addition, rs9396069 × age interactions on obesity-related traits were all nonsignificant (Supplementary Table 1), suggesting that changes in these traits by age were not dependent on the individual’s FTO genotype.

Next, we studied longitudinal change in the association between FTO and BMI during 10-year follow-up from HUNT1 to HUNT2. The FTO variant showed an association with all obesity-related quantitative traits (Supplementary Table 1). There was, however, no association between rs9396069 and ΔBMI between 1985 and 1995. This suggested that the FTO-associated relative difference of BMI is established before adulthood and then remains stable.

Confimation of the findings from HUNT-meta-analysis in 41,504 Scandinavians. Clinical characteristics of individuals from the three different cohorts are presented in Table 1. The minor allele frequencies of rs9396069 in nondiabetic individuals were 0.42, 0.41, and 0.41 in HUNT2, MPP, and MDC, respectively.

The meta-analysis demonstrated that the association between rs9396069 and type 2 diabetes was strong after adjustment for age and sex (OR 1.13 [95%CI 1.08–1.19]; P = 4.5 × 10^-5) and remained significant after BMI correction (OR 1.09 [95%CI 1.04–1.15]; P = 1.2 × 10^-4). Correction for waist-to-hip ratio or waist circumference instead of BMI did not change the results (Supplementary Fig. 2A–C). To further elucidate whether rs9396069 exerts an effect on type 2 diabetes independently of BMI, we evaluated the effect of rs9396069 according to FTO genotype during follow-up. As shown in Supplementary Fig. 3A–C, the association remained similar for incident type 2 diabetes after correction for sex and baseline age and BMI (OR 1.12 [95%CI 1.05–1.18]; P = 1.1 × 10^-3) and after correction also for ΔBMI (OR 1.11 [95%CI 1.05–1.18]; P = 1.5 × 10^-5).

The meta-analysis of the FTO-associated allele-wise effect on BMI using cross-sectional data confirmed the strong effect of the FTO SNP on BMI (0.28 kg/m^2) per risk allele [P = 2.0 × 10^-5]; Fig 2A). Furthermore, we detected no heterogeneity in the effect sizes for the FTO risk allele between the different age-groups (Fig. 2B). Finally, Fig. 3 shows the linear regression summary results between rs9396069 and ΔBMI for all HUNT and MPP individuals for whom longitudinal data were available. There was no significant difference in ΔBMI according to overall number of rs9396069 risk alleles (ΔBMI = 0.0 [−0.05, 0.05]) or in any individual age stratum (Fig. 3B). Hence, the FTO-associated effect on BMI seems to establish relatively early in life, and the relative BMI difference remains stable across adult life.

DISCUSSION

To our knowledge, this is the largest study investigating the effect of FTO sequence variants on type 2 diabetes and BMI across the whole range of adult ages and in a longitudinal perspective. In 41,504 Scandinavians, we demonstrate that a common variant of FTO does not mediate type 2 diabetes risk entirely through its influence on BMI. Although our findings are comparable with some earlier studies (25–27), they contrast previous results reported in most populations studied to date, including Europeans (1–3,8). Reasons for the diverging results could be differences in selection or recruitment of cases and control subjects between studies, differences in undetected key effects at early age, or population-specific environmental factors that may interact with the way FTO works to influence the risk of type 2 diabetes. In an attempt to capture the complex relationship between FTO, BMI, and type 2 diabetes during the life course, we performed an analysis on incident type 2 diabetes. The results remained similar in the longitudinal perspective.
TABLE 1
Clinical characteristics of the individuals from the three different cohorts

<table>
<thead>
<tr>
<th></th>
<th>HUNT MPP MDC</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>N</td>
<td>5,596</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>2,788/2,808</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.8 ± 6.6</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>10</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 4.4</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.86</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.3</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>2.0</td>
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<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>6.1</td>
</tr>
<tr>
<td>Serum HDL (mmol/L)</td>
<td>1.3</td>
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<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD. Data presented for the HUNT and MPP cohorts are follow-up measures unless otherwise stated. All data presented for the MDC cohort are baseline measures. Nonfasting plasma glucose measures were available for participants in the HUNT cohort. Data presented for the MPP cohort are follow-up measures unless otherwise stated. All data presented for the MDC cohort are baseline measures. Only nonfasting glucose measures were available for participants in the HUNT cohort.

Data from J.K. HERTEL AND ASSOCIATES. diabetes.diabetesjournals.org. DIABETES, VOL. 60, MAY 2011 1639
study both when we controlled for BMI at baseline (before diabetes was diagnosed), ΔBMI, or waist circumference and/or waist-to-hip ratio as covariates in the regression analyses. None of the covariates alone or in combination with BMI changed our results notably. FTO still conferred an increased risk for type 2 diabetes.

How sequence variation in FTO could possibly affect type 2 diabetes risk in other forms than through increased adiposity remains elusive. No associations have been reported between FTO SNPs and glucose tolerance or insulin sensitivity. A link between SNPs in FTO and altered lipid profiles has been suggested (6,9), and correlations have been observed in peripheral tissues between BMI of tissue donors and FTO mRNA expression levels (29). It is noteworthy that three recent FTO expression studies support a potential role in type 2 diabetes independently of BMI. One study found no association between FTO expression and BMI in islet cells (30). Another study reported an inverse correlation between Fto mRNA and glucose in mice after correction for body weight (31). Finally, a third study found an increase of FTO mRNA and protein levels in muscle from type 2 diabetic patients compared with healthy lean control subjects or BMI-matched obese nondiabetic individuals (32). The latter also suggests that increased FTO expression in type 2 diabetic patients contributes to reduced mitochondria oxidative capacities, lipid accumulation, and oxidative stress, all associated with type 2 diabetes. It is also possible that the rs9939609 SNP (or a SNP in strong LD) affects another gene in the region, which has the potential to alter type 2 diabetes risk independently of BMI (33).

FIG. 1. Meta-analysis plots of association between FTO and type 2 diabetes comprising 4,317 subjects with type 2 diabetes and 37,187 control subjects. A: Meta-analysis plot of association between FTO rs9939609 and type 2 diabetes after correction for age and sex (allelic OR 1.13 [95%CI 1.08–1.19]). B: Meta-analysis plot of association between FTO rs9939609 and type 2 diabetes after correction for age, sex, and BMI (allelic OR 1.09 [1.04–1.15]). We observed a tendency toward heterogeneity between the samples (P = 0.064), and the variation in the estimate attributable to heterogeneity was calculated to 63.7%. The ORs for the overall estimates were calculated using a fixed-effect model with inverse variance. The weighting (%weight) represents the inverse variance of each studies’ effect estimator.
The association between \textit{FTO} sequence variants and BMI is not established at birth (2,34) but seems to evolve gradually before adulthood (2,35,36). It is not clear how \textit{FTO} genotype affects BMI after adolescence and develops during the life course (10–18), although a recent longitudinal Finnish study suggests that the effect may continue into adulthood since they found an association between rs9939609 and BMI at age 31, which could not be explained by the BMI at age 14 (18). Using cross-sectional and longitudinal designs, we identified in the three Scandinavian populations that the relative difference in mean BMI among individuals with different rs9939609 genotypes remains surprisingly stable across all adult ages. Hence, because our study primarily comprised individuals that were above 30 years of age (98.7%), current evidence suggest that the \textit{FTO} variant increases BMI in the first 2 to 3 decades of life.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Meta-analysis plot of the \textit{FTO}-associated allele-wise effect on BMI using cross-sectional data. The results included in the meta-analysis are from regression analysis adjusted for age, sex, and diabetes status. The weighting (% weight) represents the inverse variance of each study’s effect estimator. A: Meta-analysis plot comprising all 41,504 individuals. No heterogeneity between the cohorts was detected ($P = 0.242$), and the overall allelic effect was estimated to 0.28 kg/m$^2$. B: Meta-analysis plot comprising all 41,504 individuals stratified on 10-year age strata. Moderate heterogeneity was, however, observed in two of the subgroups.}
\end{figure}
and from then on the BMI difference between the genotypes becomes more or less constant throughout life. Nevertheless, it remains to be seen whether other relevant factors such as diet and physical activity may interact and modify the susceptibility to obesity by the \( FTO \) variants during the life course (37–39).

In summary, we have replicated that a common variant in the \( FTO \) gene alters type 2 diabetes risk but find that this association is partly independent of the effect on BMI. Our data further demonstrate that the weight gain as a result of the \( FTO \) risk variant occurs during youth and that the BMI difference according to the \( FTO \) genotype persists at the same level throughout life, setting the threshold for BMI.

**ACKNOWLEDGMENTS**

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Association. The MDC study was supported by project grants from the Swedish Research Council, the European Foundation for the Study of Diabetes, the Novo Nordisk and Albert Pählsson Foundations, a Linnaeus grant to the Lund University Diabetes Centre, and the Knut and Alice Wallenberg Foundation. The MPP study was supported by grants from the Swedish Research Council (including Linneé grant 31475113580), the Heart and Lung Foundation, the Diabetes Research Society, a Nordic Center of Excellence Grant in Disease Genetics, the Diabetes Program at the Karolinska Institute, and the European Foundation for the Study of Diabetes, the Pählsson Foundation, the Crafoord Foundation, the Novo Nordisk Foundation, the European Network of Genomic and Genetic Epidemiology, and the Wallenberg Foundation. L.G. has been a consultant for and served on advisory boards for sanofi-aventis, GlaxoSmithKline, Novartis, Merck, Tethys Bioscience, and Xoma and received lecture fees from Eli Lilly and Novartis. No other potential conflicts of interest relevant to this article were reported.

J.K.H. and S.J. designed the study, wrote the manuscript, researched data, contributed to the discussion, and reviewed and edited the manuscript. E.S. and A.J. researched data and edited the manuscript. R.T.L. contributed to the discussion and reviewed and edited the manuscript. C.G.P.P. researched data and contributed to the discussion. P.M.N. contributed to the discussion and reviewed and edited the manuscript. G.R. researched data. K.M. researched data and reviewed and edited the manuscript. K.H. researched data, contributed to the discussion, and reviewed and edited the manuscript. O.M. reviewed and edited the manuscript. L.G. contributed to the discussion and reviewed and edited the manuscript. A.M. designed the study, contributed to the discussion, and reviewed and edited the manuscript. M.O.-M. researched data and reviewed and edited the manuscript. P.R.N. designed the study, contributed to the discussion, and reviewed and edited the manuscript.

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**Supplementary Table 1.** Association results between the *FTO* SNP rs9939609 and obesity-related quantitative traits in 5,596 individuals from the HUNT2 cohort.

<table>
<thead>
<tr>
<th>Traits</th>
<th>n</th>
<th>Effect size*</th>
<th>SE</th>
<th>P-value†</th>
<th>P-value SNP - age interaction‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 1985 (baseline)</td>
<td>4625</td>
<td>0.218</td>
<td>0.083</td>
<td>0.008</td>
<td>0.209</td>
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<tr>
<td>BMI 1995 (follow-up)</td>
<td>5596</td>
<td>0.269</td>
<td>0.082</td>
<td>0.001</td>
<td>0.185</td>
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<tr>
<td>BMI 1985-95</td>
<td>4625</td>
<td>-0.019</td>
<td>0.051</td>
<td>0.716</td>
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<td>Waist-hip ratio</td>
<td>5552</td>
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<td>0.001</td>
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<tr>
<td>Waist circumference</td>
<td>5552</td>
<td>0.607</td>
<td>0.204</td>
<td>0.003</td>
<td>0.385</td>
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<tr>
<td>Hip circumference</td>
<td>5553</td>
<td>0.417</td>
<td>0.163</td>
<td>0.010</td>
<td>0.204</td>
</tr>
</tbody>
</table>

*All effect sizes represent the change in trait per risk allele.
†Age, gender and diabetes status were included as covariates in the regression models.
‡An additional SNP-age interaction term was introduced in the regression model to detect whether age modifies the associations.
Supplementary Table 2. Association results between the FTO SNP rs9939609 and serum lipid measures in the HUNT2, MPP and MDC cohorts individually, and in the HUNT2-MPP-MDC combined analysis. A) Linear regression models corrected for age, gender and diabetes status. B) Linear regression models corrected for age, gender, diabetes status and BMI.

<table>
<thead>
<tr>
<th>Traits</th>
<th>HUNT2</th>
<th>MPP</th>
<th>MDC</th>
<th>Combined</th>
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<tr>
<td></td>
<td>N</td>
<td>Effect size</td>
<td>SE</td>
<td>P-value</td>
</tr>
<tr>
<td>A)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Triglycerides</td>
<td>5583</td>
<td>0.037</td>
<td>0.010</td>
<td>$2.0 \times 10^{-4}$</td>
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<tr>
<td>Cholesterol</td>
<td>5584</td>
<td>0.003</td>
<td>0.004</td>
<td>0.48</td>
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<tr>
<td>HDL-C</td>
<td>5582</td>
<td>-0.017</td>
<td>0.005</td>
<td>$2.0 \times 10^{-3}$</td>
</tr>
<tr>
<td>B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Triglycerides</td>
<td>5583</td>
<td>0.027</td>
<td>0.009</td>
<td>$5.0 \times 10^{-3}$</td>
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<tr>
<td>HDL-C</td>
<td>5582</td>
<td>-0.013</td>
<td>0.005</td>
<td>0.02</td>
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</table>

All serum lipids data were log transformed (natural) for normality.
All effect sizes represent the change in trait per risk allele.
The estimates of the combined effects were calculated using a fixed-effect model with inverse variance.
Supplementary Figure 1. Scatter-plots showing the individual BMI values by age and FTO rs9939609 genotype for the HUNT2 subjects. The corresponding fitted curves are estimated by the locally weighted least squares method (LOWESS). Red, blue and green dots and smoothed curves represent those subjects homozygote for the risk allele, heterozygote and those without the risk allele, respectively. Note that the scatter-plots at the right are truncated and only contain BMI values between 20-35 kg/m². The Lowess regression curves, however, are based on the whole range of BMI values (14.7 - 51.7 kg/m²) shown to the left. Panel A, B and C are scatter-plots with smoothed curves for BMI by age and genotype for all subjects combined, individuals without diabetes and for those with type 2 diabetes, respectively.
Supplementary Figure 2. Meta-analysis plots of association between FTO and type 2 diabetes, comprising 4,317 subjects with type 2 diabetes and 37,187 control subjects. Panel A: Meta-analysis plot of association between FTO rs9939609 and type 2 diabetes after correction for age and gender (allelic OR 1.13, 95% CI 1.08–1.19). Panel B: Meta-analysis plot of association between FTO rs9939609 and type 2 diabetes after correction for age, gender and waist-to-hip ratio (allelic OR 1.12, 95% CI 1.07–1.17). Panel C: Meta-analysis plot of association between FTO rs9939609 and type 2 diabetes after correction for age, gender and waist circumference (allelic OR 1.11, 95% CI 1.06–1.16). We observed a tendency towards heterogeneity between the samples ($P = 0.04–0.09$) in the meta-analyses, and the variation in the estimates attributable to heterogeneity was calculated to 63.7%, 58.2% and 69.3% for panel A, B and C, respectively. The ORs for the overall estimates were calculated using a fixed-effect model with inverse variance. The weighting (% weight) represents the inverse variance of each studies' effect estimator.
Supplementary Figure 3. Meta-analysis plots of association between FTO and risk to develop incident type 2 diabetes, comprising 3,143 subjects with incident type 2 diabetes during follow-up and 16,092 control subjects from the HUNT and MPP cohorts. Panel A: Meta-analysis plot of association between FTO rs9939609 and incident type 2 diabetes after correction for gender and baseline age (allelic OR 1.16, 95% CI 1.10-1.22, \( P=3.2\times10^{-8} \)). Panel B: Meta-analysis plot of association between FTO rs9939609 and type 2 diabetes after correction for gender and baseline age and BMI (allelic OR 1.12, 95% CI 1.05-1.18, \( P=1.1\times10^{-4} \)). Panel C: Meta-analysis plot of association between FTO rs9939609 and incident type 2 diabetes after correction for gender, baseline age and BMI and delta of BMI (allelic OR 1.11, 95% CI 1.05-1.18, \( P=1.5\times10^{-4} \)). The ORs for the overall estimates were calculated using a fixed-effect model with inverse variance. The weighting (% weight) represents the inverse variance of each studies' effect estimator.
SUPPLEMENTARY DATA