**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

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**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 life span 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; P = 4.5 × 10⁻¹⁰) and the risk to develop incident type 2 diabetes (OR 1.16; P = 3.2 × 10⁻⁸). 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 × 10⁻²⁰), 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.

Genomewide association studies (GWAS) have identified a strong correlation between BMI and FTO single nucleotide polymorphisms (SNPs) (1–4), which have been extensively reproduced in different study 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 ≥20) of a Norwegian population-based health survey (Nord-Tromsø Health Study) (19). 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 >7.0 mmol/L.

The Malmö Diet and Cancer (MDC) cohort (20) with baseline examinations from 1991 to 1996 consisted of 28,449 individuals. All men born between 1923 and 1945 and all women born between 1923 and 1950 from Malmö were included.
invited. Diabetes diagnosis at baseline was self-reported or diagnosed if fasting plasma glucose was $\geq 7.0$ mmol/L.

In the Malmo Preventive Project (MPP) cohort (21), 33,346 subjects from Malmo 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 $\geq 7.0$ mmol/L.

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

### 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 rs9939609 in HUNT2. This association remained significant after correction for BMI (OR 1.19 [95%CI 1.09–1.19]; $P=4.5 \times 10^{-8}$) and remained significant after BMI correction (OR 1.10 [95%CI 1.00–1.17]; $P=1.0 \times 10^{-4}$). The meta-analysis demonstrated that the association between rs9939609 and type 2 diabetes was strong after adjustment for age and sex (OR 1.13 [95%CI 1.08–1.19]; $P=4.5 \times 10^{-8}$) and remained significant after BMI correction (OR 1.09 [95%CI 1.04–1.15]; $P=1.2 \times 10^{-4}$; Fig. 2A and B). 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 rs9939609 exerts an effect on type 2 diabetes independently of BMI, we evaluated the risk to develop incident type 2 diabetes 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]; $P=1.1 \times 10^{-4}$) and after correction also for ΔBMI (OR 1.11 [95%CI 1.05–1.18]; $P=1.5 \times 10^{-4}$).

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/m² per risk allele [$P=2.0 \times 10^{-18}$]; 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 rs9939609 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 rs9939609 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 controls 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...
TABLE 1

Clinical characteristics of the individuals from the three different cohorts

| Cohort | Type 2 diabetes | No type 2 diabetes |
|--------|-----------------|-------------------|
| N      | N               | N                 |
| All    | N               | N                 |
| HUNT   | N               | N                 |
| MPP    | N               | N                 |
| MDC    | N               | N                 |

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 as a result of no available follow-up measures. Only nonfasting glucose measures were available for participants in the HUNT cohort.

**Diabetes**

| Characteristic            | HUNT | MPP | MDC |
|---------------------------|------|-----|-----|
| N                         | 1,543| 2,054| 13,876|
| Age (years)               | 72.0 | 67.9 | 56.7 |
| Follow-up time (years)    | 10.0 | 12.0 | 17.8 |
| BMI baseline (kg/m²)      | 26.8 | 29.5 | 25.6 |
| Waist-to-hip ratio        | 0.86 | 0.9 | 0.85 |
| Waist circumference (cm)  | 90.3 | 95.8 | 88.2 |
| Serum triglycerides (mmol/L) | 2.0 | 2.5 | 1.8 |
| Serum cholesterol (mmol/L) | 6.1 | 6.2 | 6.1 |
| Serum HDL (mmol/L)        | 1.3 | 1.6 | 1.4 |
| Fasting plasma glucose (mmol/L) | 6.8 | 9.6 | 5.7 |

**Data**

| Characteristic            | HUNT | MPP | MDC |
|---------------------------|------|-----|-----|
| N                         | 4,053| 2,054| 13,876|
| Age (years)               | 72.0 | 67.9 | 56.7 |
| Follow-up time (years)    | 23.5 | 24.5 | 23.4 |
| BMI baseline (kg/m²)      | 26.8 | 29.5 | 27.1 |
| Waist-to-hip ratio        | 0.86 | 0.9 | 0.92 |
| Waist circumference (cm)  | 90.3 | 95.8 | 94.8 |
| Serum triglycerides (mmol/L) | 2.0 | 2.5 | 1.8 |
| Serum cholesterol (mmol/L) | 6.1 | 6.2 | 6.1 |
| Serum HDL (mmol/L)        | 1.3 | 1.6 | 1.4 |
| Fasting plasma glucose (mmol/L) | 6.8 | 9.6 | 5.7 |

**MDC**

| Characteristic            | N    | N   |
|---------------------------|------|-----|
| N                         | 19,258|
| Age (years)               | 57.6 |
| Follow-up time (years)    | 6.5  |
| BMI baseline (kg/m²)      | 25.7 |
| Waist-to-hip ratio        | 0.85 |
| Waist circumference (cm)  | 83.2 |
| Serum triglycerides (mmol/L) | 2.0 | 2.5 | 1.8 |
| Serum cholesterol (mmol/L) | 6.1 | 6.2 | 6.1 |
| Serum HDL (mmol/L)        | 1.3 | 1.6 | 1.4 |
| Fasting plasma glucose (mmol/L) | 6.8 | 9.6 | 5.7 |
the longitudinal 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), but we could not confirm this in our meta-analysis (Supplementary Table 2). It has been suggested that rs9939609 affects the primary allelic FTO transcript levels (28), 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 non-diabetic 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).
The association between *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 *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 suggests that the *FTO* variant increases BMI in the first 2 to

### FIG. 2. Meta-analysis plot of the *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/m². B: Meta-analysis plot comprising all 41,504 individuals stratified on 10-year-age strata. No heterogeneity between the subgroups was detected ($P = 0.378$). Moderate heterogeneity was, however, observed in two of the subgroups.

| Cohort | N          | Effect (95% CI) | % Weight |
|--------|------------|------------------|----------|
| HUNT   | 5,596      | 0.27 (0.11, 0.43) | 10.35    |
| MPP    | 15,930     | 0.24 (0.17, 0.31) | 50.48    |
| MDC    | 19,978     | 0.33 (0.25, 0.42) | 39.17    |
| Overall ($f^2 = 29.6\%, p = 0.242$) | | 0.28 (0.23, 0.33) | 100.00   |

Test for overall effect: $Z = 10.64, P = 2.0 \times 10^{-26}$

| Effect (unit change in BMI per risk allele) |
|--------------------------------------------|
| -0.6 | -0.4 | -0.2 | 0 | 0.2 | 0.4 | 0.6 | 0.8 | 1 | 1.2 | 1.4 |

| Cohort | Effect (95% CI) | % Weight |
|--------|------------------|----------|
| Age 20–29 | 0.62 (−0.05, 1.30) | 0.56    |
| HUNT    | −0.04 (−0.67, 0.58) | 0.63    |
| MPP     | 0.27 (−0.19, 0.73) | 1.19    |
| Subtotal ($f^2 = 50.0\%, p = 0.158$) | |    |
| Age 30–39 | 0.07 (−0.41, 0.54) | 1.15    |
| HUNT    | 0.33 (0.20, 0.47) | 14.21   |
| MPP     | 0.31 (0.19, 0.44) | 19.35   |
| Subtotal ($f^2 = 11.4\%, p = 0.288$) | |    |
| Age 40–49 | 0.33 (−0.15, 0.81) | 1.11    |
| HUNT    | 0.22 (0.13, 0.31) | 28.53   |
| MPP     | 0.26 (0.10, 0.41) | 10.77   |
| Subtotal ($f^2 = 7.1\%, p = 0.341$) | |    |
| Age 50–59 | 0.54 (0.12, 0.98) | 1.42    |
| HUNT    | 0.50 (0.27, 0.73) | 7.80    |
| MPP     | 0.44 (0.30, 0.58) | 12.68   |
| Subtotal ($f^2 = 59.1\%, p = 0.087$) | |    |
| Age 60–69 | 0.54 (0.12, 0.98) | 1.42    |
| HUNT    | 0.44 (0.30, 0.58) | 12.68   |
| MPP     | 0.36 (0.26, 0.47) | 21.70   |
| Subtotal ($f^2 = 0.0\%, p = 0.679$) | |    |
| Age 70–79 | 0.09 (−0.27, 0.44) | 2.05    |
| HUNT    | 0.18 (−0.19, 0.06) | 0.56    |
| MPP     | 0.26 (0.09, 0.42) | 9.54    |
| Subtotal ($f^2 = 0.0\%, p = 0.431$) | |    |
| Age 80–89 | 0.45 (0.26, 0.65) | 2.70    |
| HUNT    | 0.45 (0.26, 0.65) | 2.70    |
| MPP     | 0.45 (0.26, 0.65) | 2.70    |
| Subtotal ($f^2 = 0.0\%, p = . . .$) | |    |
| Heterogeneity between groups: $p = 0.378$ | |    |
| Overall ($f^2 = 16.6\%, p = 0.264$) | 0.28 (0.23, 0.33) | 100.00  |
3 decades of life, 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.

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FIG. 3. Meta-analysis plot of the FTO-associated effect on BMI differences using longitudinal data from the HUNT and MPP study. 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 20,464 individuals with follow-up data on BMI. No heterogeneity between the cohorts was detected \( (P = 0.892) \), and the overall allelic effect for the FTO SNP on BMI difference over a period of time was estimated to 0 kg/m\(^2\). B: Meta-analysis plot comprising all 20,464 individuals stratified on 10-year-age strata. Each age stratum reflects the age at baseline. No heterogeneity between the subgroups was detected \( (P = 0.967) \). Moderate heterogeneity was, however, observed in two of the subgroups.
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