

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; $P = 4.5 \times 10^{-8}$) and the risk to develop incident type 2 diabetes (OR 1.16; $P = 3.2 \times 10^{-8}$). 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; $P = 2.0 \times 10^{-26}$), with no heterogeneity between different age-groups. We found no differences in change of BMI over time according to rs9939609 risk alleles, neither overall (Δ BMI = 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 ≥ 20) of a Norwegian population-based health survey (Nord-Trøndelag 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 >8.0 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

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Received 20 September 2010 and accepted 17 February 2011.

DOI: 10.2337/db10-1340

This article contains Supplementary Data online at <http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db10-1340/-/DC1>.

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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.

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

SNP selection, genotyping, and quality control. Because the reported obesity-associated *FTO* SNPs are in strong to perfect linkage disequilibrium (LD) (pairwise $r^2 > 0.8$; HapMap; CEU, release 21), we included rs9939609, reported by the first GWAS (2), as proxy. We genotyped HUNT2 subjects by MassARRAY *iPLEX* System (SEQUENOM, San Diego, CA). Duplicate concordance rate was 99.7% ($N = 3,761$). MDC individuals were genotyped using MassARRAY *iPLEX* System or a TaqMan assay (Applied Biosystems, Foster City, CA). Individuals (249 total) were genotyped with both methods (99.4% allelic concordance rate). A total of 8,175 individuals were genotyped twice (allelic concordance rate 99.3%). MPP subjects were genotyped by TaqMan assay with duplicate concordance rate 99.7% ($N = 7,926$). The final genotyping success rates were 99.7, 99.2, and 97.2%, in HUNT2, MPP, and MDC, respectively. The *FTO* SNP was in Hardy-Weinberg equilibrium (P value > 0.05) in all cohorts.

Statistical analysis. We used logistic regression to investigate the association between type 2 diabetes and *FTO* genotype under an additive model. Age, sex, different combinations of BMI, waist circumference, and waist-to-hip ratio were included as covariates. In HUNT2 and MPP, follow-up measures were used unless otherwise stated. In MDC, baseline measures were used because of no available follow-up. To evaluate the risk of developing incident type 2 diabetes according to the three *FTO* genotypic classes, we designed a case-control study using only subjects who were healthy at baseline. Those developing type 2 diabetes during follow-up were defined as cases and the rest as control subjects. We used logistic regression models corrected for sex, baseline age, and BMI. In a second step, we included the change in BMI over time (Δ BMI) as an additional cofactor.

To analyze the association between *FTO* genotype and BMI, we used linear regression models assuming additive effects of allele dosage with adjustment for age, sex, and diabetes status. Logarithmic transformation of BMI values did not change the results; thus, only results using nontransformed BMI are presented. To assess whether the allele-wise increase in BMI differed across different adult ages, we performed individual analysis in every 10-year age stratum in the cross-sectional and longitudinal datasets. Finally, meta-analysis was performed to combine the regression coefficients (per allele change in BMI) with their standard errors from within the three cohorts and for each specific age-group. Interstudy heterogeneity and heterogeneity between different age-groups were estimated using Cochran's Q test and the I^2 statistic. Overall estimates were calculated using a fixed-effect model with inverse variance.

We performed statistical analyses by PLINK (22) and Stata SE v10.0 (Stata, Brownsville, TX) or SPSS (version 18; SPSS Inc., Chicago, IL). Meta-analysis statistics and plots were produced using the METAN module (23) developed for Stata and with GWAMA (Genome-Wide Association Meta-Analysis) software (24).

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 1.09–1.30]; $P = 1.8 \times 10^{-5}$). 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 rs9939609 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 that the *FTO*-associated allele-wise increase in BMI persisted at the same level throughout life (Supplementary Fig. 1). In addition, rs9939609 \times 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 rs9939609 and Δ BMI between 1985 and 1995. This suggested that the *FTO*-associated relative difference of BMI is established before adulthood and then remains stable. **Confirmation 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 rs9939609 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 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. 1A 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 Δ BMI (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 [$P = 2.0 \times 10^{-26}$]; 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 Δ BMI for all HUNT and MPP individuals for whom longitudinal data were available. There was no significant difference in Δ BMI according to overall number of rs9939609 risk alleles (Δ BMI = 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

TABLE 1
Clinical characteristics of the individuals from the three different cohorts

	HUNT						MPP						MDC					
	All	N	Type 2 diabetes	No type 2 diabetes	N	All	Type 2 diabetes	N	Type 2 diabetes	All	N	Type 2 diabetes	All	N	Type 2 diabetes			
Individuals (n)	5,596	—	1,543	—	4,053	—	15,930	—	2,054	—	13,876	—	19,978	—	720	—	19,258	—
Sex (male/female)	5,596	2,788/2,808	1,543	726/817	4,053	2,062/1,991	15,930	10,335/5,595	2,054	1,604/450	13,876	8,731/5,145	19,978	6,529/13,449	720	364/356	19,258	6,165/13,093
Age (years)	5,596	59.8 ± 17.1	1,543	67.9 ± 12.0	4,053	56.7 ± 17.8	15,930	45.5 ± 6.9	2,054	45.0 ± 6.3	13,876	45.6 ± 7.0	19,978	57.7 ± 8.4	720	61.3 ± 7.3	19,258	57.6 ± 8.5
Follow-up time (years)	4,625	10	1,421	10	3,204	10	15,930	23.5 ± 4.2	2,054	24.5 ± 3.4	13,876	23.4 ± 4.3	—	—	—	—	—	—
BMI baseline (kg/m ²)	4,625	26.8 ± 4.4	1,421	29.5 ± 4.8	3,204	25.6 ± 3.7	15,925	24.3 ± 3.3	2,054	26.2 ± 3.8	13,871	24.0 ± 3.1	19,978	25.8 ± 4.1	720	28.1 ± 4.7	19,258	25.7 ± 4.1
BMI (kg/m ²)	5,596	27.3 ± 4.6	1,543	29.3 ± 4.8	4,053	26.6 ± 4.1	15,843	27.1 ± 4.1	2,038	29.3 ± 4.6	13,805	26.8 ± 3.9	—	—	—	—	—	—
Waist-to-hip ratio	5,552	0.86 ± 0.1	1,530	0.89 ± 0.1	4,022	0.86 ± 0.1	15,820	0.92 ± 0.1	2,030	0.97 ± 0.1	13,790	0.91 ± 0.1	19,959	0.85 ± 0.1	717	0.9 ± 0.1	19,242	0.84 ± 0.1
Waist circumference (cm)	5,552	90.3 ± 12.2	1,530	95.8 ± 11.8	4,022	88.2 ± 11.6	15,829	94.8 ± 12.2	2,030	102.1 ± 12.1	13,799	93.7 ± 11.8	19,963	83.5 ± 13.2	718	93.4 ± 13.8	19,245	83.2 ± 13.0
Serum triglycerides (mmol/L)	5,583	2.0 ± 1.3	1,534	2.5 ± 1.6	4,049	1.8 ± 1.1	15,921	1.3 ± 0.8	2,052	1.6 ± 1.2	13,869	1.2 ± 0.7	3,228	1.4 ± 0.9	124	2.2 ± 1.5	3,104	1.4 ± 0.8
Serum cholesterol (mmol/L)	5,584	6.1 ± 1.3	1,534	6.2 ± 1.3	4,050	6.1 ± 1.3	15,923	5.6 ± 1.1	2,052	5.2 ± 1.1	13,871	5.7 ± 1.1	3,229	6.2 ± 1.1	124	6.2 ± 1.0	3,105	6.2 ± 1.1
Serum HDL (mmol/L)	5,582	1.3 ± 0.4	1,533	1.2 ± 0.4	4,049	1.4 ± 0.4	15,915	1.4 ± 0.4	2,052	1.2 ± 0.4	13,863	1.4 ± 0.4	3,188	1.4 ± 0.4	119	1.2 ± 0.4	3,069	1.4 ± 0.4
Fasting plasma glucose (mmol/L)*	5,582	6.8 ± 3.3	1,533	9.6 ± 4.2	4,049	5.7 ± 1.9	15,921	5.8 ± 1.3	2,050	7.9 ± 2.4	13,871	5.5 ± 0.5	3,228	6.0 ± 1.9	125	12.3 ± 4.7	3,103	5.7 ± 1.0

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.

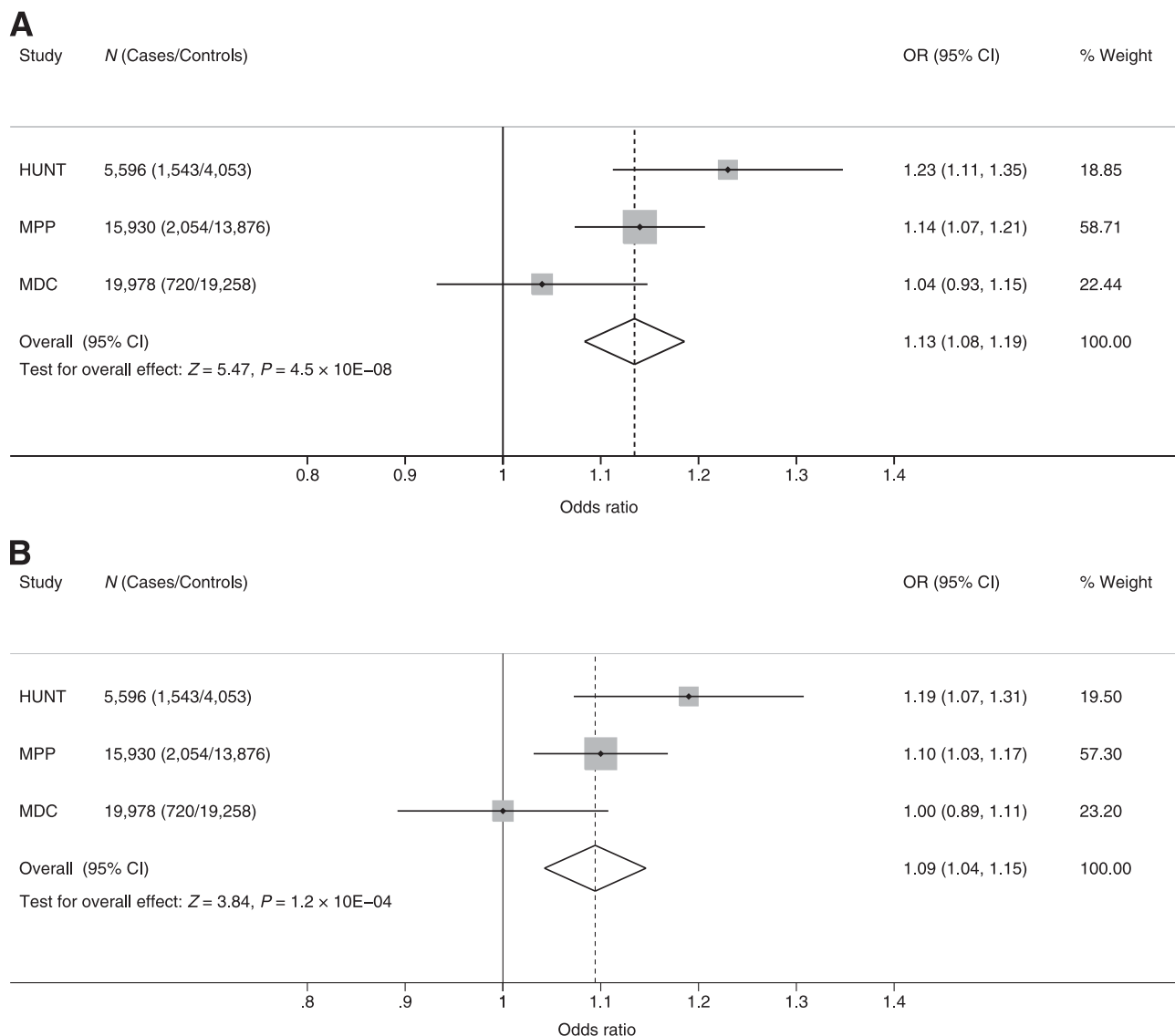


FIG. 1. Meta-analysis plots of association between *FTO* and type 2 diabetes comprising 4,317 subjects with type 2 diabetes and 37,187 control subjects. A: Meta-analysis plot of association between *FTO* rs9939609 and type 2 diabetes after correction for age and sex (allelic OR 1.13 [95% CI 1.08–1.19]). 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.

study both when we controlled for BMI at baseline (before diabetes was diagnosed), Δ BMI, 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 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).

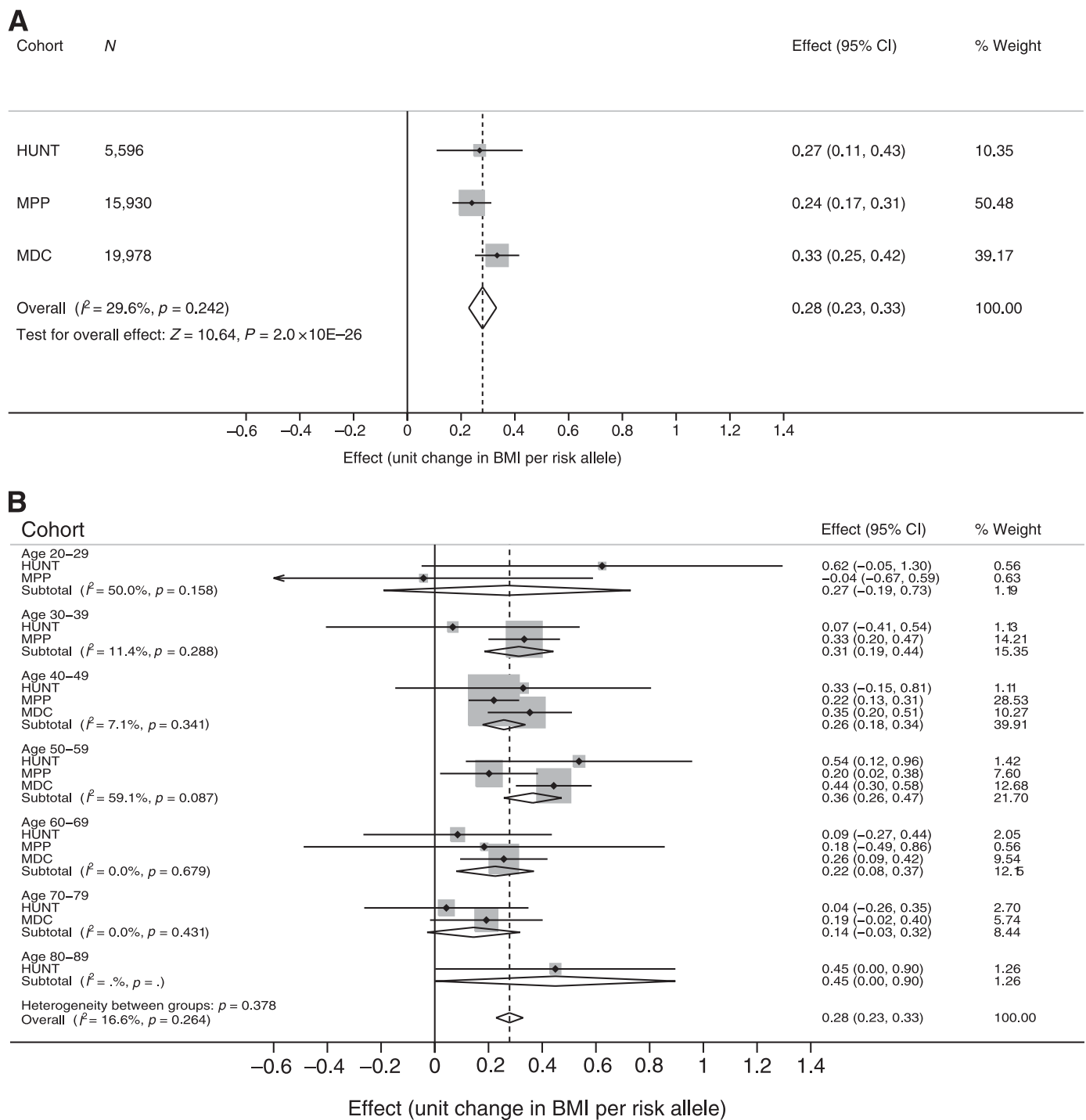


FIG. 2. Meta-analysis plot of the *FTO*-associated allele-wise effect on BMI using cross-sectional data. The results included in the meta-analysis are from regression analysis adjusted for age, sex, and diabetes status. The weighting (%weight) represents the inverse variance of each study's effect estimator. **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/m^2 . **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.

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 suggest that the *FTO* variant increases BMI in the first 2 to 3 decades of life,

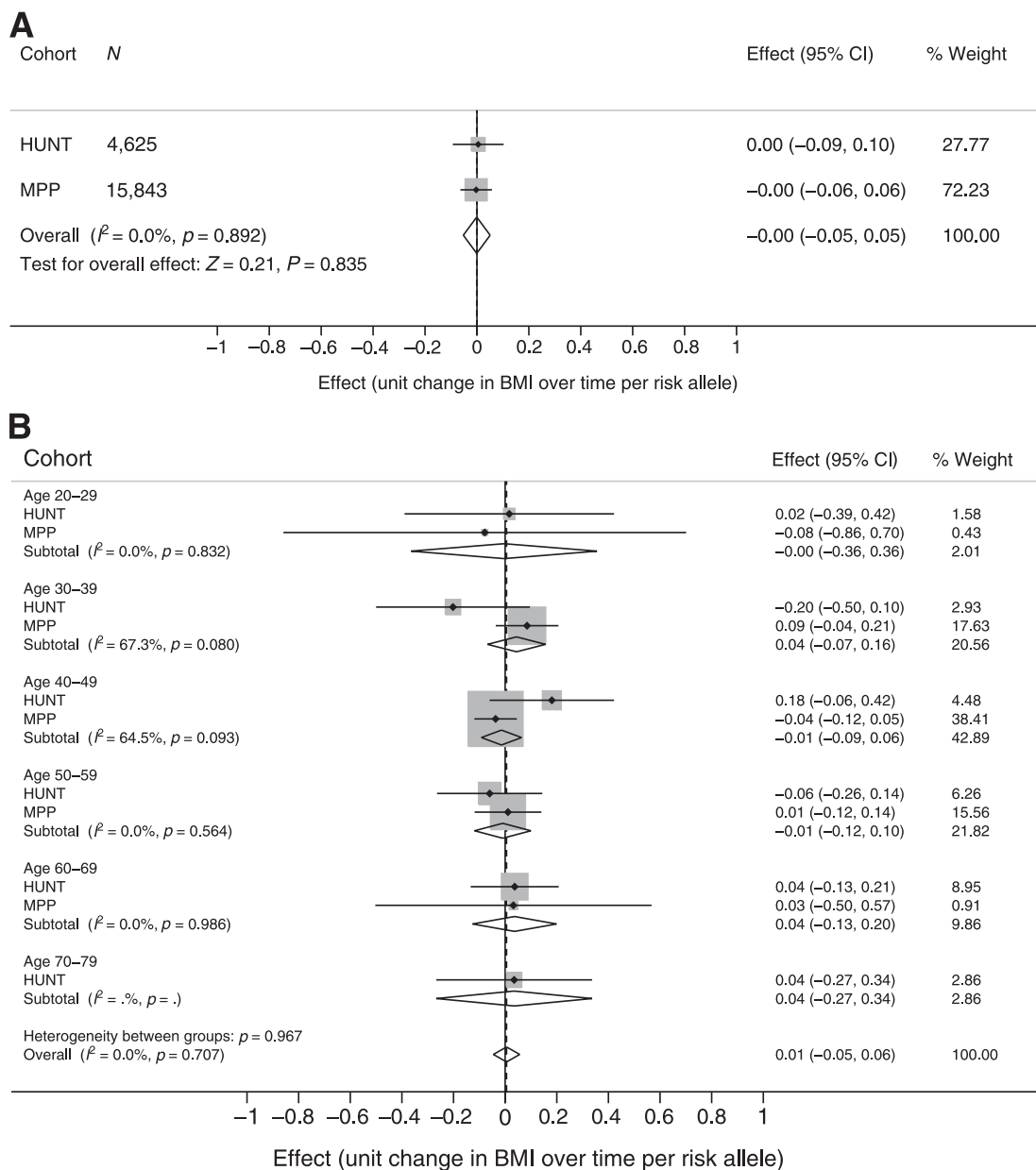


FIG. 3. Meta-analysis plot of the *FTO*-associated effect on BMI differences using longitudinal data from the HUNT and MPP study. The results included in the meta-analysis are from regression analysis adjusted for age, sex, and diabetes status. The weighting (%weight) represents the inverse variance 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/m². **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.

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

The HUNT study was supported in part by funds from the University of Bergen, Haukeland University Hospital, Helse Vest, Innovest, and the Research Council of Norway. Genotyping was in part provided by the CIGENE technology platform (Ås, Norway), which is supported by the Functional Genomics Programme (FUGE) of the Research Council of Norway. HUNT is a collaboration between the HUNT Research Center at the Norwegian University of Science and Technology, Levanger; the Norwegian Institute for Public Health; and the Nord-Trøndelag County Council. The diabetes part of HUNT was partly supported by funds from GlaxoSmithKline Norway and the Norwegian Diabetes

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 Pålsson 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 Linné 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 Lund University, the European Foundation for the Study of Diabetes, the Pålsson Foundation, the Craaford 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 reviewed 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. V.L. researched data 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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