IMPACT OF *FTO* GENOTYPES ON BODY MASS INDEX AND WEIGHT IN POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction

- Recently identified *FTO* rs9939609 SNP and some other variants have been associated with increased weight, BMI and several related traits as well as with increased odds of type 2 diabetes.
- PCOS is a common endocrine disorder affecting 6-12% of reproductive age women that present with hyperandrogenism, ovulatory dysfunction and polycystic ovaries. Moreover PCOS women are frequently obese, which correlates with increased risk of insulin resistance, type 2 diabetes and cardiovascular diseases.
- Recently, a study of the Polish population,[1] followed by other analyses, demonstrated a substantially larger impact of the *FTO* rs9939609 polymorphism on weight in PCOS women as compared to the previously reported weight difference in the general population.
- Our study aims to perform a systematic review and meta-analysis to fully define the effect of the *FTO* gene variants on BMI and weight in PCOS women.

Methods

- Systematic literature search was performed in order to identify all studies on PCOS women regardless of their design, methodology and language, provided that patients were genotyped for the *FTO* rs9939609 SNP or for other SNPs in strong LD.
- Databases and sources searched up to April 2011 included:
  - MEDLINE (via PubMed),
  - EMBASE,
  - Cochrane's CENTRAL,
  - webpages of associations dealing with diabetes (ADA, EASD).
- Two authors independently reviewed the articles at each stage of the selection.

Statistical analyses

- Per allele effect change on BMI and body weight were calculated and rank-based Z-transformation or inverse normal transformation was performed in order to present data in standard deviation units.
- Fixed-effect model inverse variance meta-analysis was used to combine effect measures.
- Both, Chi-squared test for heterogeneity and Z-test were used in order to statistically compare the effect of the *FTO* mutations on BMI in the subset of PCOS women with the reference results of genome-wide association studies obtained from the general female population:
  - Unpublished data provided by the GIANT Consortium investigating an association between rs1558902 *FTO* polymorphism and BMI increase in 109,955 adult women of European ancestry
  - Published data from Frayling et al. investigating eleven cohorts, including over 18,800 adult women [2]
- Results were presented with 95% confidence intervals (95% CI) if not otherwise stated.

Results

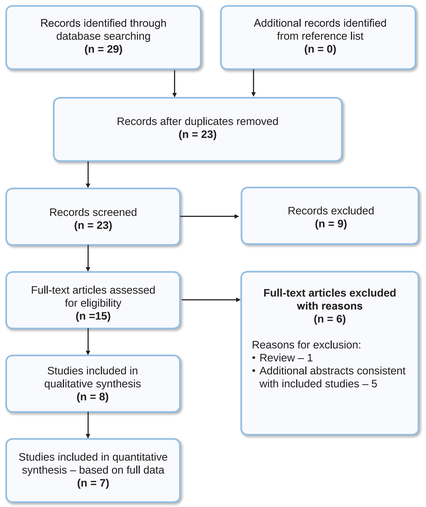
Study flow

- A total number of 29 records were identified as a result of a systematic search of which 23 records were subjected for analysis after removal of duplicates. In the following steps six further publications were excluded due to reasons presented in PRISMA diagram. Finally, 8 relevant studies were included in the analysis (Figure 1).

Study characteristics

- Included studies were conducted in six European countries (Austria, Czech Republic, Germany, Poland, Romania, United Kingdom) and in the United States [1,3-8]. All of the study subjects were Caucasian, except for American cohort, where Caucasians constituted 91%, Hispanics 3%, African Americans 1%, and 5% were of unknown ethnicity. Clinical characteristics of the investigated populations are shown in Table 1. Overall, Caucasians represented 97% of the entire group. Patients were genotyped for the *FTO* rs9939609 SNP in six studies and for rs1421085 in one of them[8]. The study size ranged from 136 to 469, with a total of 2,548 PCOS women included in the analysis for whom at least BMI or body weight were available. Of these, 762 were TT homozygote patients, 1,253 had an AT/CT genotype, and 533 were AA/CC homozygotes, for rs9939609 and rs1421085 respectively. The genotype distribution was generally consistent across the cohorts, and the observed A/C allele frequency ranged from 42% to 52%. Genotype distribution of all cohorts was consistent with HWE.
- Mean age of the PCOS population ranged from 25 to 32 years old. Mean BMI ranged from 26.44 to 35.37 kg*m^{-2} with patients weighing least in Austria and the heaviest study cohort originating from the United States. Mean weight ranged from 73.01 to 95.76 kg. Data regarding body weight were not available for one study [8].

Figure 1. Systematic literature search according to PRISMA



Anthropometric traits

- Data regarding BMI were available for a total of 2,510 PCOS patients (746 were TT homozygotes; 1,239 - AT/CT heterozygotes, and 525 with AA/CC genotype). A strong association between the FTO variants and BMI was revealed. Each additional copy of the effect allele increased BMI by a mean of 0.19 Z-score units ([95% CI 0.13, 0.24]; p = 2.26*10^{-11}), equivalent to ~1.62 kg*m^{-2} (Figure 2). No heterogeneity between the studies was noted (p = 0.9217, I2 = 0%). This association remained almost unaffected even after data was adjusted for age (0.18 Z-score units [95% CI 0.12, 0.23]; p = 1.30*10^{-10}, equivalent to 1.55 kg*m^{-2}).
- Data regarding body weight were available for a total of 2,161 PCOS patients (648 were TT homozygotes; 1,068 - AT heterozygotes, and 445 with AA genotype). Meta-analysis of the seven cohorts revealed that in PCOS patients each additional copy of the effect allele was associated with a body weight increase of a mean of 0.20 Z-scores ([95% CI 0.14, 0.26]; p = 1.02*10^{-10}), which is equivalent to ~4.79 kg. This effect was highly consistent across the studies and no evidence of heterogeneity was observed (p = 0.9388, I2 = 0%).

Comparison between PCOS and general female population

- The observed *FTO*-associated BMI increase in PCOS women was larger than the corresponding effect found in the 109,955 women from the GIANT Consortium cohort (p = 0.0002) (Figure 3A). The association between examined polymorphisms and BMI in PCOS women was also stronger than reported previously by Frayling et al.[2] for the general female population (p = 0.0146) (Figure 3B). When PCOS data was corrected for age, the impact of FTO on BMI remained significantly greater as compared effect sizes of both the GIANT Consortium cohort (p = 0.0005) and the female cohort described by Frayling et al. (p = 0.0298).

Conclusions

- In conclusion, our meta-analysis based on eight distinct cohorts shows that the *FTO* polymorphisms per allele effect on BMI and weight seems to be more than two times greater than the effect found in large population based studies. Our results suggest that the metabolic context or specific polygenic background of PCOS modifies the influence of *FTO* on weight and BMI.

Table 1. Characteristics of included studies

Population	Country	Total (N)	Mean age	Caucasian ethnicity (%)	TT carriers			AT carriers			AA carriers			A allel frequency (±SD)	Test for HWE (p value)
					n (%)	Weight	BMI	n (%)	Weight	BMI	n (%)	Weight	BMI		
Wehr et al. [4]	Austria	288	28.05 (6.30)	100%	87 (30%)	70.17 (18.19)	25.21 (6.31)	150 (52%)	73.70 (20.80)	26.85 (7.48)	51 (18%)	75.70 (19.47)	27.27 (6.65)	0.44 (0.02)	0.32
Vcelak et al. [7]	Czech Republic	243	27.65 (7.07)	100%	80 (33%)	70.46 (15.96)	25.18 (5.47)	116 (48%)	77.01 (19.59)	27.61 (7.09)	47 (19%)	79.80 (16.93)	28.61 (6.13)	0.43 (0.02)	0.67
Kowalska et al. [1]	Poland	136	25.36 (5.45)	100%	35 (26%)	72.58 (20.19)	26.07 (6.78)	61 (45%)	78.20 (20.73)	28.61 (7.01)	40 (29%)	82.92 (20.49)	29.72 (6.71)	0.52 (0.03)	0.24
Barber et al. [5]	UK	445	32.27 (7.02)	100%	129 (29%)	74.93 (20.37)	27.57 (7.30)	218 (49%)	79.17 (23.42)	28.88 (8.54)	98 (22%)	82.21 (22.15)	30.00 (8.04)	0.47 (0.02)	0.74
Tan et al. [6]	Germany	383	27.97 (6.44)	100%	110 (29%)	86.57 (23.07)	30.85 (7.60)	191 (50%)	85.45 (24.06)	30.46 (8.42)	82 (21%)	97.16 (30.89)	34.45 (9.97)	0.46 (0.02)	0.96
Ewens (PCOS Cases) et al. [3]	USA	395	27.25 (7.02)	91%	130 (33%)	86.16 (27.07)	32.07 (9.83)	197 (50%)	87.33 (24.93)	32.21 (8.75)	68 (17%)	97.30 (27.98)	35.64 (9.82)	0.42 (0.02)	0.65
Ewens (PCOS Families) et al. [3]	USA	469	27.60 (5.81)		139 (30%)	94.56 (22.90)	34.99 (8.10)	233 (50%)	91.71 (23.22)	34.46 (8.36)	97 (21%)	106.72 (26.79)	38.23 (9.36)	0.46 (0.02)	0.97
Attaoua et al. [8]	France, Romania	189	24.68 (5.59)	100%	52 (28%)	N/A	27.96 (7.67)	87 (46%)	N/A	27.99 (6.72)	50 (26%)	N/A	30.82 (6.54)	0.49 (0.03)	0.28

Figure 2. Inverse variance (IV) meta-analysis of per allele (A/C) effect increase in log-BMI Z-score units.

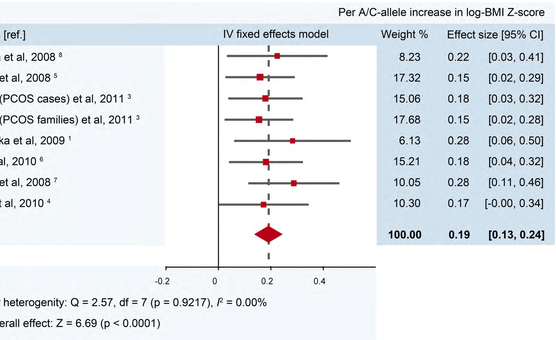
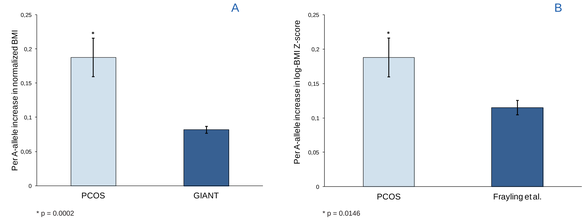


Figure 3. Comparison of effect FTO A/C allele on BMI between PCOS women and the general female population from the GIANT Consortium (A) and the study of Frayling et al. (B). Data expressed in either rank-based inverse normally transformed BMI (A) or log transformed BMI Z-scores (B). Error bars represent standard error (SE).



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Abbreviations

BMI	body mass index	HWE	Hardy-Weinberg equilibrium
FTO	fat mass and obesity associated gene	PCOS	polycystic ovary syndrome