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Association of Genetic Risk Scores with Body Mass Index in Swiss Psychiatric Cohorts

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ABSTRACT

OBJECTIVE: Weight gain is associated with psychiatric disorders and/or with psychotropic drug treatments. We analyzed in three psychiatric cohorts under psychotropic treatment the association of weighted genetic risk scores (wGRS) with Body Mass Index (BMI) by integrating BMI-related polymorphisms from Candidate Gene approach and Genome Wide Association Studies (GWAS).

MATERIALS AND METHODS: wGRS of 32 polymorphisms previously associated with BMI in general population GWAS and 20 polymorphisms associated with antipsychotics induced weight gain were investigated in three independent psychiatric samples.

RESULTS: wGRS of 32 polymorphisms were significantly associated with BMI in the psychiatric sample 1 (n=425) and were replicated in another sample (n=177). Those at the percentile 95 (p95) of the score had 2.26 and 2.99 kg/m^2 higher predicted BMI compared to individuals at the percentile 5 (p5) in the Sample 1 and in the Sample 3 (p=0.009, p=0.04, respectively). When combining all samples together (n=750), a significant difference of 1.89 kg/m^2 predicted BMI was found between p95 and p5 individuals at 12 months of treatment. Stronger associations were found among men (difference: 2.91 kg/m^2 of predicted BMI between p95 and p5, p=0.0002) whereas no association was found among women. wGRS of 20 polymorphisms was not associated with BMI. The wGRS of 52 polymorphisms and the clinical variables (age, sex, treatment) explained 1.99% and 3.15%, respectively of BMI variability.

CONCLUSION: The present study replicated in psychiatric cohorts previously identified BMI risk variants obtained in GWAS analyses from population-based samples. Gender specific analysis should be considered in further analysis.

Key words: Psychotropic drugs, Genetic Risk Score, Psychiatry, Body Mass Index

INTRODUCTION

Obesity has become a major public health concern, its prevalence increasing dramatically over the last decades. Obesity is a complex disease that results from imbalance of energy intake and energy expenditure, being highly influenced by an individual's lifestyle or environment (i.e. diet, physical activity) and also by genetic predisposition [1]. Twin and family studies reported 40%-80% of heritability in obesity [2, 3]. Several forms of monogenic obesity have been described, especially those related to leptin-melanocortin pathways [4, 5]. The most prevalent form of obesity, however, is the polygenic or common obesity, which results from the combined effect of common genetic variants as well as additional rare variants, copy number variants, and epigenetic changes [6]. Among psychiatric populations, the risk of developing obesity and related problems is increased compared to the general population [7]. Several factors have been attributed to this increased obesity risk, such as the illness, the lifestyle and/or the medication [8, 9].

Since their introduction onto the market, second generation antipsychotics (SGA) have been widely used over first generation antipsychotics (FGA), as they clearly show an advantage in terms of reduced risks of extrapyramidal side-effects, as well as some advantages for the treatment of negative symptoms. However, most SGA can induce strong metabolic disturbances in particular as a consequence of the dual antagonism on serotonin and dopamine receptors and its effect on food intake regulation [10]. Over the last decade, pharmacogenetics of psychotropic-induced weight gain has been widely studied through hypothesis-driven candidate gene approaches. The most studied and best-replicated polymorphisms focused on dopamine and serotonin receptors [11, 12]. Additionally, other genes implicated in leptin-melanocortin pathways (e.g. *LEP, LEPR, MC4R, NPY*), endocannabinoids (*CNR1*) or genes involved in fatty acids and cholesterol production (*SCARB1, INSIG2*) showed an association with weight gain

among psychiatric cohorts treated with antipsychotics (see review [13]). Recently, research conducted in our laboratory showed other candidate genes which could potentially induce weight gain among psychiatric populations under psychotropic treatment. These genes code for enzymes involved in metabolic pathways (PCK1, 11βHSD1) [14-16] for receptors (MCHR2, IRS2 and PPARGC1A) and for transcriptional co-activators (CRTC1, CRTC2) involved in energy balance, appetite regulation and glucose homeostasis [17-21].

With the emergence of genome wide association studies (GWAS), thousands of new polymorphisms associated with obesity and metabolic phenotypes have been elucidated. In particular, the associations with Body Mass Index (BMI) and/or obesity in the *FTO* [22-25], *MC4R* [26-28]*, and TMEM18* [23, 24, 28, 29] genes have been widely replicated in general populations. The largest BMI meta-analysis of GWAS conducted to date in general populations reported 97 polymorphisms [30]. These variants also included 32 previously reported loci [31] that have been replicated in other cohorts and different ethnicities [32-34]. Individually, these variants have shown little effect on the BMI [31]. As an alternative way of testing individual Single Nucleotide Polymorphisms (SNP) effects, Genetic Risk Scores (GRS) summarize risk-associated variations across the genome by aggregating information from multiple-risk SNPs [35] with small effects increasing the consistency and power to determine genetic risk in polygenic diseases (i.e. obesity) [36]. To date, GRS methods have been used in diabetes [37], schizophrenia [38] and obesity [31] among other diseases. Studies on obesity have been conducted in adults [36, 39] or children from the general population [40, 41] and recently two studies were conducted among depressed patients [42, 43]. The aim of the present study was to determine if GRS built from previous BMI and/or weight gain related variants from GWAS and candidate genes (CG) were associated with BMI in three independent psychiatric samples. Additionally, we wanted to analyze if previous variants related to diabetes (21 SNPs) and

psychiatric disorders (9 SNPs) also showed an association with BMI, since these diseases seem to share some genetic components with obesity [8, 44, 45].

MATERIALS and METHODS

Samples Description

Psychiatric samples

Sample 1 (n=425) consisted of an on-going follow up study which started in 2007 in the psychiatric ward from the Lausanne University Hospital already described elsewhere [46]. Briefly, 425 Caucasian patients starting psychotropic treatment including atypical antipsychotics, mood stabilizers and/or mirtazapine were recruited. Anthropometric parameters such as weight, height and waist circumference were measured. Other demographic covariates (i.e. sex, age and ethnicity) as well as history of treatment (treatment duration, psychotropic treatment) were obtained from medical files or during the interview. Medical questionnaires were filled in and blood samples were collected at baseline and at 1, 2, 3, 6, 12 months after initiating psychotropic treatment according to guidelines [47, 48]. Patients switching to one of the studied treatments were also included. BMI (in kg/m^2), the outcome in the present study, was used as a continuous variable and whenever required, stratified in 3 categories as normal (BMI<25 kg/m^2) overweight (25 ≥BMI<30, kg/m^2) and obese (BMI≥30 kg/m^2). 21% of patients had the first psychotic episode and/or were diagnosed within the first year of study inclusion (first episode and newly diagnosed (FEND) patients).

Two other psychiatric samples were used as replication. They consisted of two retrospective studies from outpatient settings in Geneva and in Lausanne (Sample 2=148, Sample 3=177, respectively). Both samples included patients receiving atypical antipsychotics and/or mood

stabilizers (i.e. aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, lithium and/or valproate). The Geneva study started in 2007 in an outpatient Geneva setting and patients recruited had been under psychotropic treatment for at least 3 months. In the Lausanne study (Sample 3 started in 2010, inclusions ongoing), most of the patients had been treated for more than one year in a Lausanne outpatient setting. For both studies, blood samples were collected and questionnaires were filled out during one of the routine checkup. Weight, height, waist circumference, serum lipids and/or glucose were measured and several clinical variables (e.g. treatment, treatment duration) were recorded. Baseline weight (before the current psychotropic treatment) was extracted from medical files or self-reported. Further description of these samples has been published elsewhere [46].

Psychiatric diagnoses for the three samples were made according to ICD-10 classification criteria. The main diagnostic groups were [F20.0-F24.9] & [F28-F29]: psychotic disorders; [F25.0-F25.9]: schizoaffective disorders; [F30.0-F31.9]: bipolar disorders; [F32.00-F33.9]: depression. The latest introduced psychotropic medication was considered as the main psychotropic treatment. Written informed consent was provided by all individuals or by their legal representatives and the studies were approved by the ethics committee of the corresponding centers.

General population-based sample

The Genetic Investigation of Anthropometric Traits Consortium (GIANT) performed a meta-analysis of GWAS data with a discovery set of 123,865 individuals of European ancestry from 46 studies for height [49], BMI [31] and Waist to Hip Ratio (WHR) [50]. This general population-based sample was used to obtain β-coefficients (allele effect) which assigned weights to each variant when building the genetic risk scores.

SNP selection, genotyping and construction of Genetic Risk Scores

The Initial 32 polymorphisms selected for the present study had been associated with BMI in a GWAS meta-analysis conducted in an adult general population [31]. All selected variants reached GWAS significance ($p<5x10^{-8}$) (S1 Table). Another 20 SNPs which had been previously related to antipsychotic-induced weight gain through candidate gene approach were also selected [13]. From the reviewed variants, only SNPs or proxies of SNPs genotyped in our sample and in GIANT, and only those in the literature reaching significant results in both genders were retained for the analysis. A detailed description of the SNPs considered can be found in S2 Table.

Finally, we considered two meta-analyses of GWAS based on 21 SNPs associated with type 2 diabetes (8,130 cases and 38,987 controls, S3 Table) and another one based on 9 SNPs associated with 5 major psychiatric disorders (final dataset: 33,332 cases and 27,888 controls, S4 Table) including schizophrenia, bipolar disorder, major depressive disorder, autism and attention deficit-hyperactivity disorder [51, 52]. In order to avoid indirect correlation between variants (i.e. in high Linkage Disequilibrium (LD) correlation), which is one of the problems when constructing GRS [53], and to avoid overrepresentation of a particular gene, only one SNP per gene was considered. Selection was made by selecting the SNP with the lowest P-value. We verified that the resulting SNPs were not in LD. Note that this approach is analogous to an LD-based pruning, but we typically select less SNPs by ignoring secondary (independent) SNP contributions from the same gene (allelic heterogeneity). The study protocol was approved by the ethics committees of the recruiting centers and all patients gave written informed consent for the genetic analysis. DNA was extracted from blood samples as described by the manufacturer protocols using Flexigene DNA kit and QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG, Switzerland).

Genotyping of 895 Caucasian patients was performed using the Illumina 200K Cardiometabochip (Illumina, San Diego, CA). Briefly, the Cardiometabochip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200'000 SNPs from regions identified by large scale meta-analyses of GWAS for metabolic and cardiovascular traits [54]. A Quality Control was done for the genotyped SNPs. Polymorphisms or proxies were chosen based on genotype availability in the Cardiometabochip and GIANT cohort. In addition, samples were excluded from the analysis if sex was inconsistent with genetic data from X-linked markers, and when genotype call rate was <0.96, gene call score <0.15 and minor allele frequency (MAF) <0.05. GenomeStudio Data Analysis Software was used to export results generated by Illumina CardiometaboChip. Additionally, the *rs7799039* from the *LEP* gene largely associated with antipsychotic-induced weight gain [55] and which was not available in Cardiometabochip was genotyped by KBioscience Institute in United Kingdom using the novel fluorescence-based competitive allele-specific PCR technology (KASP™). Details about this technology are available at: http://www.lgcgenomics.com/genotyping/kasp-genotyping-chemistry/. Out of the 895 Caucasian genotyped individuals, 750 were finally analyzed (145 patients excluded due to missing data).

Among the several existing methods to build a GRS, it has been shown in disease risk modeling that weighted GRS methods are preferred to the simple count method when relative risks vary among SNPs [56]. SFig 1 represents the distribution of the weighted genetic score by the number of risk alleles (unweighted score) calculated for each individual in the whole cohort showing that weighted and unweighted scores are not perfectly correlated, thus highlighting the importance of weighting each risk allele using weighted Genetic Risk Score (w-GRS) methods. The w-GRS for selected SNPs was calculated as previously described [31]. In summary, genotypes from each SNP were coded as 0, 1 or 2 according to the number of BMI risk alleles. Then, each polymorphism was weighted by its β-coefficient (allele effect) based on the

assumption that all SNP of interest have independent effects and contribute in an additive manner to BMI. Allele effect on BMI was obtained performing lookups from the summary statistics of an independent population sample (GIANT consortium, n=123,865), thus preserving homogeneity of β-coefficient calculations (S5 Table) for all SNPs included in the genetic score.

Statistics

Principal Components of Ancestry was used to assess ethnicity and only Caucasians were considered in the analysis. Hardy-Weinberg Equilibrium (HWE) was determined for each polymorphism by a chi-square test. HWE and genotype frequencies are shown in supplementary tables (S1 and S2 Tables). P-values equal or less than 0.05 were considered as statistically significant and Bonferroni correction for multiple tests was applied when necessary. Initially, individual SNP effects on BMI were calculated for Sample 1. Genotypes were analyzed in an additive model of inheritance except for one SNP (*HSD11β1 rs3753519C>T*) which had too few homozygous for the variant allele (n=7) and a dominant model was used. Secondly, a GRS was built and tested in Sample 1 and it was further tested for replication in 2 other psychiatric samples (samples 2 and 3). Finally, in order to determine the general effect of the GRS on BMI, we combined all samples since they were similar overall in terms of individual's origin (Lausanne and Geneva regions), type of treatment, age, and diagnostic. Due to interdependence between observations (i.e. BMI) made on the same individual over time, a Generalized Linear Mixed Model (GLMM) was fitted using the MASS library of R language [57, 58] to assess influence of genetic parameters on BMI in a model adjusted by age, sex, main psychotropic treatment and treatment duration. The appropriate link function we chose for the BMI variable is the inverse function which is the canonical link function for the Gamma family. GLMMs combine both linear mixed models (which incorporate random effects) and generalized linear models (which deal with non-normal data by using link functions and exponential family)

[59]. The glmmPQL function of the MASS library uses the Penalized Quasi-Likelihood in order to estimate model parameters [60]. Finally, predicted BMI differences were calculated at baseline, 12 and 24 months of treatment between the percentile 95 (the upper extreme of an unfavorable genetic background) and percentile 5 (the lower extreme of an unfavorable genetic background) of the GRS. In order to preserve homogeneity within samples and to deal with treatment durations when combining all samples together (i.e. shorter treatment duration up to 12 months in sample 1), predicted BMI was obtained at baseline and at 12 months of treatment. The corresponding 95% confidence intervals (95%CI) were calculated. Some exploratory analyses were also performed to obtain the explained variance of BMI by genetic and non genetic covariates in the psychiatric Sample 1 for a subgroup of individuals aged between 18 and 65 years. A Generalized Additive Mixed Model (GAMM) was used to deal with complex and non-linear BMI evolution in time and presence of multiple observations per individual introducing interdependence among observations. A random effect at the subject level was also introduced to take the dependence structure of observed data into account. The GAMMs were fitted using the mgcv package of R (settings were fixed at package defaults). To be more conservative the uncertainty of estimated parameters was assessed by 10’000 bootstraps on individuals [57, 61, 62]. Individuals with missing data or genotypes were excluded from the analysis (see supplementary methods for further details).

RESULTS

Population description

Table 1 presents the characteristics of Sample 1 (n=425) and replication Samples 2 and 3 (n_1= 148, n_2= 177). All samples together consisted of 750 Caucasian individuals with 50% of men and a median age of 45 years (range: 13 - 97 years). Sample 2 had the highest obesity (BMI≥ 30 kg/m^2) prevalence (35% compared to 18% in Samples 1 and 3, p=0.006). Sample 1 had the lowest olanzapine and clozapine prescription (11% and 8%, respectively compared to 16% and 14% in Sample 2, respectively, and 12% and 9% in Sample 3, respectively, p=0.001) as well as the shortest treatment duration (6 months) when compared to samples 2 and 3 (27 and 36 months, respectively). S6 and S7 Tables show the characteristics of the combined cohort stratified by gender and by FEND patients, respectively. Men were younger than women (median 40 years versus 49 years, respectively, p=0.0001) and had higher BMI at baseline (24.6 kg/m^2 versus 24.1 kg/m^2 in men and women, respectively, p=0.004). Besides, treatment duration was longer for men than women (9 months compared to 6 months, respectively, p=0.05) (S6 Table).

Genetic analysis

Genotype analysis

S1 and S2 Tables list the 32 and 20 SNPs from GWAS and CG studies, respectively, analyzed in the psychiatric samples. All of them were in Hardy-Weinberg equilibrium after multiple test correction (p-corrected<0.001). Thirty-two previously reported SNPs associated with BMI in the general population [31] were analyzed in Sample 1. One SNP located in *CADM2* gene showed

a nominal association with BMI over time (p-value=0.01) (Table 2). At 12 months of treatment, *rs13078807* polymorphism showed a 1.04 BMI units increase per additional risk allele. Twenty other SNPs were selected from CG studies associated with psychotropic induced-weight gain and two of them (i.e. *HSD11β1-rs3753519*, *CRTC2-rs8450*) showed an association with BMI (difference of predicted BMI of -2.35 units for *rs3753519* at 12 months of treatment between patients homozygous for the variant allele and wild types and 0.69 units of BMI increase per additional risk allele for *rs8450*, p-values: 0.00001, 0.04, respectively) (Table 2).

Genetic Risk Score analysis

When combining all 32 GWAS SNPs in a weighted GRS (w-GRS 32), the score was significantly associated with BMI in Sample 1 (p=0.009), in Sample 3 (p=0.04) and also in the three combined samples (p=0.002, see Table 3). In Sample 1, those at the percentile 95 (p95) of the GRS (i.e. a high genetic risk score) had 2.26 units more of predicted BMI when compared to those individuals at the percentile 5 (p5) of the GRS (low genetic risk score) at 12 months of treatment. Results were similar in Sample 3 and when all samples were combined together at 24 and 12 months of treatment (difference of predicted BMI between p95 and p5 of the GRS: 2.99 and 1.89 units, respectively). A higher effect on BMI was found among men when analyses were stratified by sex in the combined sample (interaction sex*GRS p<0.10): individuals at the p95 score had 2.91 units more of predicted BMI when compared to individuals at the p5 score at 24 months of treatment (p-value: 0.0002). For the subgroup of FEND patients a difference of predicted BMI of 3.79 units was observed between individuals at the p95 and p5 of the GRS (p=0.008) (Table 3). Fig 1 shows the evolution of BMI (non adjusted) over time between extreme percentiles (low genetic risk; p5 versus high genetic risk; p95). Additionally, predicted BMI differences between p10 and p90 extremes are presented in S8 Table and S2 Figure.

When pooling all samples together, one unit increase of the risk allele at 24 months of treatment in the GRS was associated with an increase of BMI of 0.19 units (p=0.011). Among men, this increase in BMI was of 0.30 units (p=0.0001) whereas in women it was of 0.08 (p=0.38).

Unlike to what we found with GWAS SNPs, when the 20 CG SNPs were combined in a weighted GRS (w-GRS 20), no association with BMI was observed in the whole sample (p=0.46) (S9 Table).

Finally, the 20 CG SNPs were combined with the 32 GWAS SNPs in another w-GRS (w-GRS 52) (S10 Table). w-GRS 52 was significantly associated with BMI in Sample 1 (p=0.01), Sample 3 (p=0.04) and when combining all samples (p=0.001). Only a trend was observed in Samples 2 and 3 when pooled together (p=0.06). Thus, an individual in the p95 score had 2.08, 2.79 and 1.94 more predicted units of BMI in Sample 1 (12 months of treatment), in Sample 3 (24 months of treatment) and in all samples combined together (12 months of treatment) when compared to individuals at the p5 of the score, respectively. When analyses were stratified by gender, a significant effect was found among men at the p95 of the score who showed 3.09 more units of predicted BMI when compared to men at the p5 (p=0.0001). FEND patients who were at the top percentile (p95) had also 3.66 more units of predicted BMI when compared to patients at the p5 of the GRS (p=0.01).

GLMM according to different quartiles showed significant differences between individuals within the 3rd and 4th quartile of the GRS as compared to the 1st quartile. At 24 months of treatment, those at the 3rd and 4th quartiles had 1.84 [0.40-3.29] and 1.91 [0.51-3.32] more units of predicted BMI when compared to the 1st quartile, respectively (results not shown). Table 4 shows the characteristics for the four groups stratified by GRS quartiles. Those at the 4th quartile had higher BMI before starting and during the current psychotropic treatment (baseline

and current median BMI: 25.1 and 25.9 kg/m^2, respectively) when compared to the 1st quartile (baseline and current median BMI: 23.2 and 24.3 kg/m^2, respectively), which could be possibly explained by the interaction between genetics, previous psychiatric episodes and/or psychotropic treatments. The prevalence of baseline overweight and obesity increased in higher quartiles (i.e. 48% in 4th quartile versus 30% in 1st quartile, p=0.007). No differences of age, treatment, treatment duration, high waist circumference prevalence, diagnostic and FEND individuals distribution were observed between the different quartile groups (Table 4).

Finally, when comparing the distribution of genetic scores without adjusting by other covariates, no differences were found between men and women (S6 Table) or FEND patients (S7 Table).

Genetic Risk Scores and GWAS genes for psychiatric diseases and diabetes

The SNPs selected from GWAS associated with psychiatric diseases (i.e. schizophrenia, bipolar disorder, major depressive disorder, autism and hyper attention deficit) and diabetes were combined in two different w-GRS and tested for association with BMI. No significant results were found (results not shown).

Explained variability

We calculated the BMI variability explained by the clinical and genetic covariates in the Sample 1, for individuals from 18 to 65 years old (n=263). Thus, in our model, the genetic component considering the w-GRS 32 explained 1.97% of BMI variability whereas non genetic components such as age, sex and treatment explained 2.23%, 0.42% and 0.6%, respectively, out of the total 7.01% BMI variability explained by the model. Finally, the BMI explained variance of the 52 SNPs (32 SNPs added to the 20 SNPs) was of 1.99% whereas the important clinical variables

known to influence weight (age, sex, treatment) represented altogether 3.15% of the BMI variability.

DISCUSSION

In the present study, we found that w-GRS built from 32 polymorphisms previously associated with BMI in the general population GWAS were also significantly associated with BMI in our Sample 1, being replicated in another sample. The stronger effects were found among men and FEND patients. Some studies have replicated the association of the 32 SNPs GRS with BMI and obesity-related genotypes in different cohorts and ethnicities [32-34]. Two cross-sectional studies using a Mendelian randomization approach [42] and a case-control design [43] replicated the association of w-GRS in depressed patients. However, type of treatment, treatment duration or BMI variation over time were not taken into account, while BMI at baseline and treatment duration are known moderators of weight gain in populations under psychotropic treatment [9]. Moreover, the number of patients treated was not described in the previous studies. The present study, in contrast, includes longitudinal data considering long treatment duration (i.e. analysis has been conducted up to 24 months), type of treatment and other diagnostics in addition to depression. Explained BMI variability by GRS when including 32-SNPs GWAS GRS in our model, was slightly higher than the one reported initially in general population cohorts in the literature (1.45%) [31] or than the one found in French and Chinese general populations (1%, 0.90%, respectively). Of note, adding the 20 CG in the model did not improve the explained BMI variability (1.97% versus 1.99%). The effect on BMI per risk allele increase of the 32-SNPs GWAS GRS was similar to those reported previously (0.11 [32], 0.13 [34]) when considering both genders together. However, higher BMI increase per risk allele was found among men.

Individual SNP analyses showed few significant effects in Sample 1. Only one GWAS SNP (*rs13078807)* located in *CADM2* gene region was nominally associated with BMI. *CADM2* has been previously associated with obesity in Caucasians and other ethnicities [31, 63, 64]. Among the CG polymorphisms, 2 SNPs (*HSD11β1 rs3753519* and *CRTC2 rs8450*) were associated with BMI in Sample 1; however *rs8450* did not survive Bonferroni correction. In addition to weight gain association in psychiatric samples [16], *HSD11β1* has been associated with metabolic syndrome in a general population [14] and *CRTC2* has been associated with type 2 diabetes in Asian populations [65]. CRTC2 is a coactivator which binds to CREB and stimulates the expression of PEPCK and G6Pase and this increases hepatic gluconeogenesis through dephosphorylation [66, 67]. In addition, a deletion of CRTC2 impairs the expression of the gluconeogenic genes and the ability of glucagon to stimulate glucose production in hepatocytes [68]. On the other hand, *HSD11β1* gene codes for a microsomal enzyme catalyzing tissue regeneration of active cortisol from the inactive form cortisone [69]. It is highly expressed in metabolic tissues such as liver and adipose tissue. Increased plasma cortisol levels have been associated with visceral obesity and metabolic syndrome. An overexpression of this gene has been associated with hyperphagia and obesity in mice [70, 71].

The fact of finding stronger effects when combining all SNPs in a w-GRS could be explained by the fact that common variants have individually little effect on BMI and very large sample sizes are needed in order to detect small effects. Thus, when integrating many small variant effects in a w-GRS, the consistency and the power to detect these effects increase, even in smaller sample sizes [35]. In addition, the BMI explained variability in the whole model was 7.01%, with 1.97% of it corresponding to the w-GRS. Of note, although this is not a high percentage, it represents a 28% of the total BMI variability explained by the model. The present study is in the same line as a very recently published study concerning GWAS meta-analysis of large

population data-sets (>300 000 individuals) where the genetic component (i.e. w-GRS) explained up to 2.7% of BMI variability [30].

The w-GRS 32 SNPs could not be replicated in Sample 2. This might be tentatively explained by the fact that BMI and overweight prevalence at baseline were the highest among the 3 samples. Low BMI at baseline has been described as a risk factor for gaining weight [72]. In the same line, when analyzing the 20 CG variants previously associated with antipsychotic-induced weight gain in a w-GRS, no significant association was observed between the w-GRS and BMI. SNPs from CG studies that were selected included very heterogeneous studies, with small sample sizes and with different ethnicities, treatment and treatment durations (see S2 Table), which could explain the non significant results in our psychiatric samples. In addition, some very promising variants (i.e. *5HT$_{2C}$ receptor*) could not be included in our weighted GRS model since the allele effect (β-coefficient) calculation was not available, but when calculating unweighted GRS (in which this variant was included) results did not change significantly (p=0.22). Finally, an *a priori* use of an additive model for the effect of all variants could contribute to the negative findings.

We also found significant effects for the w-GRS 32 among FEND patients who had lower BMI and obesity prevalence at baseline and shorter treatment duration when compared to others. This is in agreement with previous studies showing that low baseline BMI and first-episode patients are known risk factors for important weight gain during psychotropic drug treatment [9]. To our knowledge, this is the first study reporting stronger effect in men when analyzing the influence of genetic scores on BMI despite the fact that gender differences regarding fat storage and metabolism have already been described [73]. This emphasizes the need to consider gender when studying obesity-related phenotypes such as BMI. In the present study, men were, on average, younger and had longer treatment duration when compared to women, which could

346 contribute to the observed gender effect as both young age and treatment duration are known
347 risk factors for important weight gain [9]. Of note, when calculating genetic risk score and
348 gender interaction, a trend was observed when all three samples where combined (p=0.09,
349 n=750). Due to the exploratory nature of these findings, further analysis including gender
350 stratification should be conducted in larger psychiatric cohorts.

351 Finally, no association was found with BMI of GRS built from SNPs obtained from psychiatric
352 disorders and diabetes GWAS. Although obesity, type 2 diabetes and psychiatric disorders are
353 known to share common etiological pathways [8], these results could be considered as negative
354 controls, since we only obtained significant BMI-GRS association results when we combined
355 previously BMI-related SNPs.
356
357 This study has some limitations which should be mentioned: weighted scores were calculated
358 from β-coefficients obtained from general population samples and the relative influence of these
359 genes might differ in psychiatric patients. Other factors influencing weight gain, such as
360 previous treatment history, were not reported. This study has been conducted in Caucasians;
361 therefore these results cannot be extrapolated to other ethnicities. Variants included in the
362 genetic score model should be consistent with their effects (i.e. tested in large sample sizes and
363 replicated effects). Finally, the 95%CI suggest that genetic effect is variable within the groups
364 and sample size should increase in order to narrow CI and improve outcome precision.
365
366 In conclusion, the present study replicated in psychiatric cohorts previously identified BMI risk
367 variants obtained in GWAS analyses from population-based samples. GRS can be a useful tool
368 to integrate multiple variants with low impact which, when tested individually, do not show any
369 significant effect. This approach can contribute to a better understanding of the genetic
370 variability of polygenic obesity in psychiatric patients and our results suggest that particular care

371 should be taken to sex-specific analyses when working with GRS. Thus, the clinical utility of the
372 w-GRS in obesity-related traits needs to be further explored in prospective studies, especially
373 among populations at high risk of developing metabolic disorders.

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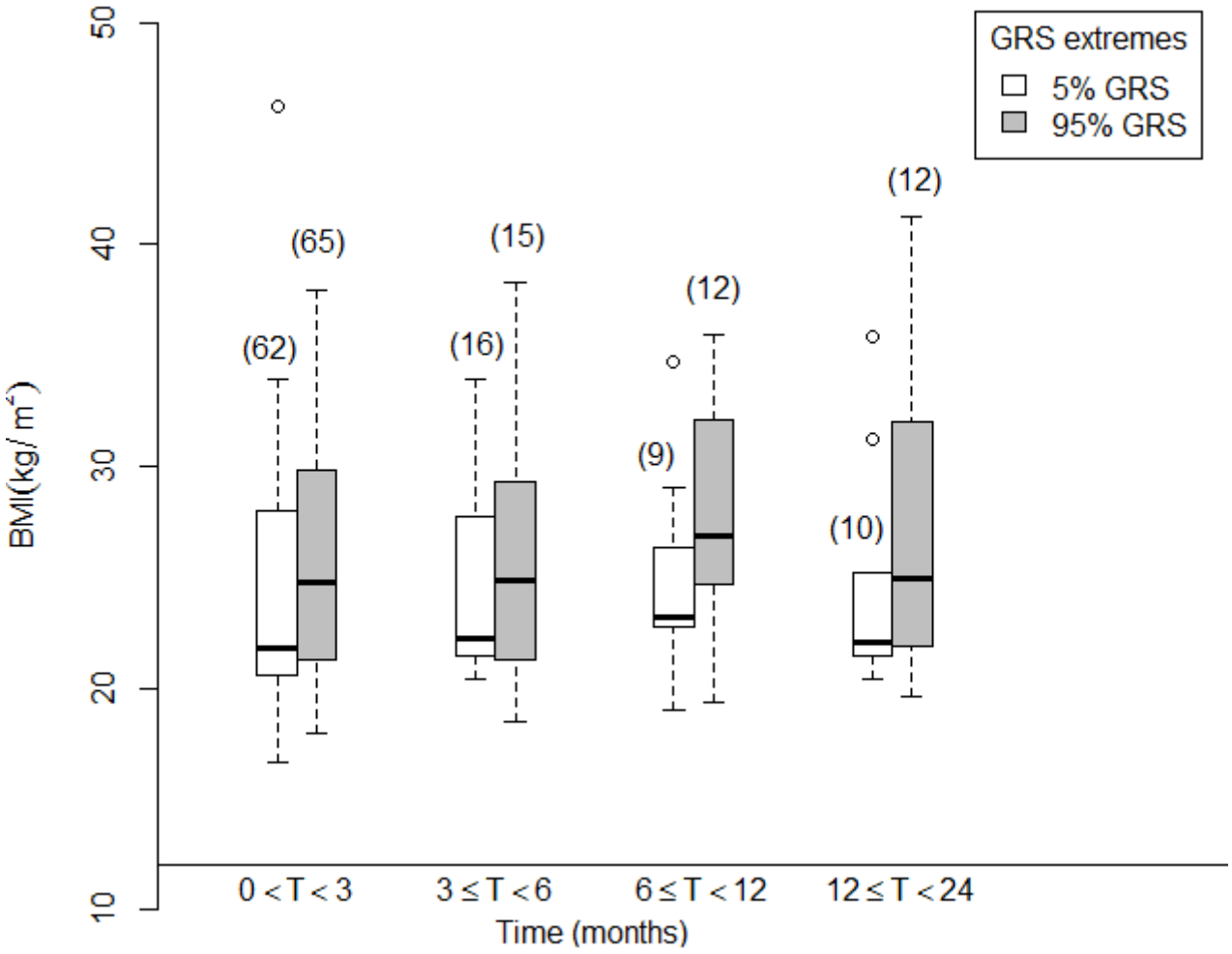
Fig 1. Evolution of BMI over time between Genetic Risk Score extreme percentiles



Boxplots show median values of BMI for each time of the treatment duration (solid horizontal line), 25th and 75th percentile values (box outline), the lowest and upper value within 1.5 Interquartile range (whiskers) and outlier values (open circles). (n) corresponds to individuals.

Table 1. Description of demographic and clinical psychiatric Caucasian samples.

Characteristics	Sample 1 n = 425	Sample 2 n = 148	Sample 3 n = 177	Combined sample n=750
Male,%	43	55	62	50
Age, median (range), years	51 (13-97)	42 (19-64)	42 (18-69)	45 (13-97)
Diagnosis				
Psychotic disorders,%	28.6	24.5	9.0	31.4
Schizo-affective disorders,%	7.3	17.0	12.1	10.3
Bipolar disorders,%	18.8	34.7	16.8	21.5
Depression disorders,%	16.4	17.0	12.7	15.7
Others diagnosis,%	28.9	6.8	14.5	21.2
Initial BMI status ‡				
BMI, median (range), kg/m^2	23 (13-44)	25 (15-46)	24 (16-46)	24 (13-46)
25 kg/m^2 ≥ Initial BMI<30 kg/m^2, %	22	37	31	28
Initial BMI≥ 30 kg/m^2, %	13	16	15	14
Current BMI status #				
BMI, median (range), kg/m^2	25 (15-50)	28 (16-40)	25 (17-43)	26 (15-50)
25 kg/m^2 ≥ Current BMI<30 kg/m^2, %	25	38	29	27
Current BMI≥ 30 kg/m^2, %	18	35	18	21
Initial waist circumference ‡				
WC, median (range), cm	87 (54-138)	--	--	87 (54-138)
High WC ≥ 94 cm (male), ≥ 88 cm (female), %	41	--	--	41
Current waist circumference #				
WC., median (range), cm	93 (57 – 162)	--	92 (73-136)	90 (57-162)
High WC ≥ 94 cm (male), 88 cm (female), %	51	--	53	51
Initial Lipid status ‡				
High LDL cholesterol, % (n) [a]	9	--	--	9
High triglycerides, % (n) [b]	18	--	--	18
Low HDL cholesterol, % (n) [c]	23	--	--	23
Current Lipid status #				
High LDL cholesterol, % (n) [a]	15	--	--	15
High triglycerides, % (n) [b]	28	--	--	28
Low HDL cholesterol, % (n) [c]	26	26	17	26
Smoker, %	46	59	76	56

Characteristics	Sample 1 n = 425	Sample 2 n = 148	Sample 3 n = 177	Combined sample n=750
Prescribed psychotropic drug[$]				
Amisulpride, %	8	-	11	7
Aripirazole, %	8	-	7	6
Clozapine, %	8	14	9	9
Olanzapine, %	11	16	12	12
Quetiapine, %	35	20	24	29
Risperidone, %	15	17	17	16
Lithium, %	8	20	12	11
Valproate, %	5	14	8	8
Treatment duration, median (range), months	6 (1-12)	27 (3-333)	36 (1-390)	12 (1-390)

ǂ Before the current psychotropic treatment

 # For Sample 2 and 3 : current observation ; for Sample 1 : last observed data

-- Missing clinical values or obtained in non fasting conditions

[a] *High LDL cholesterol : equal or higher than 4.1 mmol/L*

[b] *High triglycerides : equal or higher than 2.2 mmol/L*

[c] *Low HDL cholesterol : less than 1 mmol/L*

W.C: Waist circumference

[$] *2% of the Sample 1, was under* paliperidone treatment

Table 2. Significant results obtained from individual SNP association with BMI in the psychiatric sample 1 at baseline and at 12 months of follow-up treatment.

nearest gene	SNP	Major/minor allele	Difference of predicted BMI per risk allele increase [95% CI]		p-value
			at baseline	at 12 month of treatment	
CADM2	*rs13078807*	A>G	0.93 [0.89 – 1.97]	1.04 [-0.14 – 2.22]	**0.01**[#]
HSD11ß1	*rs3753519**	C>T	-2.11 [-3.22 – (-)1.00]	-2.35 [-3.60 – (-)1.10]	**0.00001**
CRTC2	*rs8450*	G>A	0.62 [0.28 – 1.62]	0.69 [-0.44 – 1.83]	**0.04**[#]

*CI: Confidence Interval. Predicted differences of BMI were calculated for polymorphisms that showed significant results (p-value<0.05).*a dominant model was used for this SNP(carriers of the variant allele were compared to wild type).*[#]*not significant after Bonferroni correction*

Table 3. Weighted GRS association with BMI obtained from 32 Genome Wide Association Studies SNPs.

	n	BMI difference between GRS (p95) and GRS (p5) [95% CI]			p-value
		at baseline	at 12 months	at 24 months	
Sample 1*	425	2.01 [0.52 - 3.51]	2.26 [0.48-4.04]		**0.009**
Sample 2 **	148	-0.51 [-3.02 – 2.00]	-0.61 [-3.61 – 2.40]	-0.73 [-4.67 – 3.22]	0.7
Sample 3 **	177	2.54 [0.26-4.81]	2.75 [0.23-5.27]	2.99 [-0.01 - 6.00]	**0.04**
Samples 2 and 3 **	325	1.43 [-0.27 – 3.13]	1.61 [-0.33 – 3.56]	1.82 [-0.59 – 4.24]	0.1
All samples combined	750	1.68 [0.65 - 2.72]	1.89 [0.71 - 3.06]		**0.002**
FEND patients*	116	3.29 [0.79-5.78]	3.79 [0.88-6.71]		**0.008**
Men	375	2.59 [1.45-3.74]	2.91 [1.06-4.22]		**0.0002**
Women	375	0.76 [-0.55 – 2.06]	0.84 [-0.63 – 2.32]		0.3

GRS: Genetic Risk Score, p95: percentile 95 of GRS, p5: percentile 5 of GRS.

**follow-up to 12 months of treatment. **follow-up to 24 months of treatment.*

FEND: First Episode and Newly Diagnosed Patients

Table 4. Description of 4 quartiles of GRS for 32 SNP in the combined sample.

GRS (n)	**1st quartile** 192	**2nd quartile** 170	**3rd quartile** 186	**4th quartile** 202	**p-value**
Score, mean (SD)	0.87 (0.06)	0.97 (0.02)	1.05 (0.02)	1.16 (0.07)	**0.0001**
Men, %	47	55	44	53	0.1
Age, median (range), years	47 (17-96)	47 (13-90)	48 (14-97)	48 (15-93)	0.9
Initial BMI (kg/m^2), median (range) *	23.2 (13-46)	24.6 (15-39)	25.1 (16-46)	25.1 (14-39)	**0.0005**
Current BMI (kg/m^2) #, median (range)	24.3 (16-40)	25.2 (15-40)	25.9 (16-50)	25.9 (17-41)	**0.04**
First episode and newly diagnosed patients;%	13	15	16	17	0.6
Treatment prescription					
Ami, Ari, Li, Quet, Risp	74	70	71	67	0.5
Clo, Olan, Valp	26	30	29	33	
Treatment duration, median (range), months	6 (1-23)	3 (1-21)	3 (1-24)	3 (1-24)	0.9
High waist circumference (WC ≥ 94 cm men, 88 cm women); %	40	47	49	53	0.2
Diagnostic, %					
Psychotic disorders	42	42	38	46	
Bipolar disorders	21	22	21	21	0.6
Depression disorders	17	15	17	14	

Ami: amisulpride, Ari: aripiprazole, Li: lithium, Quet: quetiapine, Risp: risperidone, Clo: clozapine, Olan: olanzapine, Valp: valproate

** Before the current psychotropic treatment*

 # Last observed data