Oxytocin pathway polygenic risk scores for severe mental disorder and metabolic phenotypes in the UK Biobank

Adriano Winterton^a, Francesco Bettella^a, Ann-Marie G. De Lange^{a,b,c}, Marit Haram^a, Nils Eiel Steen^a, Lars T. Westlye^{a,b,d}, Ole A. Andreassen^{a,d}, Daniel S. Quintana^{a,b,d*}

^a Norwegian Centre for Mental Disorders Research (NORMENT), University of Oslo and Oslo University Hospital, Oslo, Norway

^b Department of Psychology, University of Oslo, Oslo, Norway

^c Department of Psychiatry, University of Oxford, Oxford, UK

^d KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway

* Corresponding author: Daniel S. Quintana (daniel.quintana@medisin.uio.no)

Abstract

Oxytocin is a neuromodulator and hormone that is typically associated with social cognition and behavior. In light of its purported effects on social cognition and behavior, research has investigated its potential as a treatment for psychiatric illnesses characterised by social dysfunction, such as schizophrenia and bipolar disorder. While the results of these trials have been mixed, more recent evidence suggests that the oxytocin system is also linked with cardiometabolic conditions for which individuals with severe mental disorders are at a higher risk for developing. To investigate whether the oxytocin system plays a pleiotropic role in the aetiology of severe mental illness and cardiometabolic conditions, we explored oxytocin's role in the shared genetic liability of schizophrenia, bipolar disorder, type 2 diabetes and several phenotypes linked with cardiovascular disease and type 2 diabetes risk using a polygenic pathway-specific approach. Analysis of a large sample with 488,377 individuals (UK Biobank) revealed statistically significant associations across the range of phenotypes analysed. By comparing these effects to those of polygenic scores calculated from 100 random gene-sets, we also demonstrated the specificity of many of these significant results. Altogether, our results suggest that the shared effect of oxytocin system dysfunction could help explain the co-occurrence of social and cardiometabolic dysfunction in severe mental illnesses.

Introduction

Schizophrenia (SCZ) and bipolar disorders (BD) are associated with reduced life expectancies^{1,2}, partly caused by an increased risk for cardiovascular disease (CVD)³. One-third of patients with psychotic disorders suffer from metabolic syndrome (MetS)⁴, a collection of co-occurring metabolic risk factors⁵ (i.e., glucose intolerance, insulin resistance, visceral adiposity, dyslipidaemia, and hypertension) for the development of CVD and type 2 diabetes mellitus (T2D)⁵. Studies have reported a two-times higher prevalence of MetS in people with bipolar disorder or schizophrenia⁶, and this increased prevalence is comparable between males and females⁷.

In addition to lifestyle habits such as smoking, poor diet, and a lack of exercise⁸, some antipsychotic medications account for a portion of the increased prevalence of MetS risk factors in these patients⁹. However, evidence of MetS risk factors in untreated individuals with first-episode psychosis¹⁰, in antipsychotic-naïve patients¹¹ and in healthy first-degree relatives¹² suggests that the risk factors are, in part, independent from antipsychotic treatments and lifestyle factors, which point to other influences. While genetic studies support the presence of common causes predisposing to both MetS risk factors and psychotic disorders¹³, the mechanisms underpinning the shared risk for psychotic disorders and MetS remain unclear. An additional piece of the puzzle is the prevalence of loneliness and social isolation among patients with psychotic disorders—the annual rate of loneliness is approximately 2.3 times higher in patients with schizophrenia and bipolar disorder than in the general population¹⁴, and research has demonstrated a link between loneliness, MetS risk factors and cardiovascular morbidity¹⁵. However, little is known about the mechanisms underlying this association.

Emerging evidence suggests that oxytocin system dysfunction might play a pleiotropic role in the aetiology of psychotic disorders and MetS risk factors^{16–18}. Oxytocin is a versatile and multifunctional hormone and neurotransmitter associated with a variety of social

behaviours and employed in several therapeutic settings¹⁹. Animal studies have demonstrated oxytocin's critical role in maternal, sexual, feeding, and pair-bonding behaviours^{20–22}. Subsequent research has supported the effects of oxytocin administration on social behaviours in humans^{16,23} as well as its involvement in a number of metabolic and homeostatic processes²⁴. Exogenous intranasal and intravenous oxytocin administration was shown to reduce caloric intake in humans^{25,26} as well as body weight in dietarily-induced-obese rhesus monkeys through decreased food intake and increased energy expenditure and lipolysis²⁷. Oxytocin has also been shown to influence the cardiovascular system, with demonstrated effects on blood pressure, heart rate, heart rate variability, and contractility^{28–31}. However, the extent of these effects and evidence in humans has been limited.

Oxytocin pathway gene variants have been associated with features of psychotic disorders, such as social cognition and emotional processing^{32,33}. There is converging evidence that oxytocin modulates several neurotransmitter systems in the brain (e.g., dopamine, glutamate and serotonin) that have been implicated in psychotic disorders³⁴. Oxytocin administration has been shown to improve positive and negative symptoms, as well as cognitive deficits^{34,35} in patients with schizophrenia, while other studies have provided conflicting evidence^{36,37}. Despite promising initial results, some of these early findings on the effects of intranasal oxytocin have failed to replicate³⁸ and recent research has questioned the ability of exogenous oxytocin to influence social behaviour, citing issues regarding poorly understood pharmacodynamics and potential publication bias^{19,39}. While group-level studies have provided mixed findings, it is conceivable that previously diverging results may be partly explained by different experimental approaches and individual differences in treatment response⁴⁰. There is, therefore, a need to shed light on the underlying mechanisms of oxytocin in human behaviours and psychiatric disorders.

A common approach to examining the relationship between oxytocin gene variants and phenotypes of interest is to use candidate gene approaches, typically investigating the oxytocin receptor gene (*OXTR*) or *CD38*, which regulates the excretion of oxytocin⁴¹. Given

the small influence that these genetic variations exert on the analysed traits, candidate gene approaches with samples of the sizes that typically characterize these studies are statistically underpowered to precisely detect realistic true effects⁴². Consequently, most studies reporting associations between single genetic variants and behavioural phenotypes have not replicated⁴³. There are, however, over 150 genes in the oxytocin signalling pathway. A multivariate approach examining the cumulative polygenic signal across a gene-set representing relevant biological pathways will be far more likely to detect reliable effects compared to a candidate gene approach. Therefore, to explore the role of the oxytocin system in the shared genetic liability between schizophrenia, bipolar disorder, type 2 diabetes and cardiovascular risk factors, we calculated the genetic contribution of oxytocin pathway SNPs to polygenic risk for schizophrenia and bipolar disorder as well as type 2 diabetes mellitus to analyse and compare central and peripheral contributions and their associations with anthropometric and behavioural CVD risk factors. We applied this polygenic pathway-specific approach in a very large sample (UK Biobank) with 488,377 genotyped individuals with well-characterised anthropometric (BMI, waist-to-hip ratio, impedance measures of body composition) and behavioural CVD risk factors (diet, loneliness and social isolation).

Methods

Population

The UK Biobank initiative is a large-scale biobank prospective cohort established by the UK Medical Research Council and Wellcome Trust⁴⁴. This population-based study examines the influence of genetic and environmental factors on the occurrence of disease in participants in the age range of 40–69 years old, recruited between 2006–2010. The study has included approximately 500,000 participants of which 54% are female. Participants filled out questionnaires about their lifestyle, family, diet, and medical history, in addition to providing a variety of physical measures (e.g., weight). A subset of participants also filled in a mental health questionnaire online. All participants provided signed informed consent. The UK

Biobank was approved by the National Research Ethics Service North West. Specific details regarding recruitment and data collection procedures have been previously published⁴⁵. Further details regarding genotyping and quality control procedures for the UK Biobank are well documented⁴⁶. The present research has been conducted using the UK Biobank Resource under Application Number 27412.

Oxytocin Pathway SNPs

We downloaded the gene pathway consensus database (ConsensusPathDB) from the Max Planck Institute for Molecular Genetics website (cpdb.molgen.mpg.de)⁴⁷ and extracted the approved gene names annotated to the “Oxytocin signaling pathway”. We then retrieved the genomic coordinates (('chromosome_name', 'start_position', 'end_position') of the default ENSEMBL transcripts annotated to those gene names (filtering on 'hgnc_symbol') using BiomaRt (host = 'grch37.ensembl.org', path = '/biomart/martservice', dataset = 'hsapiens_gene_ensembl')⁴⁸. We complemented the transcript regions obtained with any regulatory elements annotated to the same gene names in the ORegAnno⁴⁹ database (January 2016 version) for Homo sapiens. All 1000 genomes phase 3 variants⁵⁰ found in the European sub-sample and located within the resulting genomic regions were assigned to the Oxytocin signalling pathway.

Oxytocin Pathway Polygenic Risk Score (PRS_{oxy})

We calculated three oxytocin pathway polygenic risk scores (PRS_{oxy}) using PRSice-2 (version 2.3.3)⁵¹, by limiting the calculation to SNPs belonging to the oxytocin signalling pathway in European ancestry samples, adopting a methodology similar to that of a previous report⁵². The schizophrenia PRS_{oxy} was based on a meta-analysis of the European-ancestry subset of the 2020 Psychiatric Genomics Consortium schizophrenia GWAS⁵³, the bipolar disorder PRS_{oxy} was based on a meta-analysis of the European-ancestry subset of the 2019 PGC bipolar disorder GWAS⁵⁴, and the Type 2 Diabetes mellitus PRS was based on a meta-analysis of

the European Caucasian subset of the DIAGRAM 2012 GWAS⁵⁵. For each GWAS, 2000 PRS_{oxy} scores were calculated from thresholds ranging from 5×10^{-8} to 1, in increments of 0.001. Using a permutation approach included in PRSice-2⁵¹, we determined an optimal PRSs threshold of $p < .05$ for schizophrenia (including 427 SNPs), $p < .02$ for bipolar disorder (including 198 SNPs) and $p < .4$ for type 2 diabetes mellitus (including 1107 SNPs) and used PRSs computed at these thresholds for the main analysis, after a transformation to z-scores.

Principal components PRS (PC-PRS)

In addition to using a series of oxytocin pathway PRSs based on the initial threshold, for each phenotype we also performed a principal component analysis (PCA) on the whole range of PRSs computed for each GWAS, following previously used methods^{56–58} and then using the first two oxytocin pathway PRS-Principal Components (PC_{oxy}), as in the main analysis (PC1_{oxy} and PC2_{oxy}). The first PC reweights the variants included in the PRS to achieve maximum variation over all PRS thresholds used (Supplementary fig. 1). This unsupervised approach incorporates all computed scores across a range of tuning parameters and is agnostic regarding the outcome of interest, therefore helping control Type 1 error rates⁵⁶ and capturing the greatest variation of the oxytocin pathway PRSs computed under a range of parameter settings⁵⁶.

Phenotypical variables

The following metabolically relevant variables were considered (Table 1): anthropometric and cardiovascular variables (such as BMI, waist to hip ratio and grip strength), body composition variables measured through impedanciometry, and dietary intake variables averaged from the responses to the one-day online dietary recall questionnaire. Hand grip strength in particular has shown prognostic value in a number of outcomes in adults, particularly older ones, such as physical activity, diabetes, metabolic syndrome and cardiovascular mortality^{59–61}, and BMI, waist-to-hip ratio, diet and body composition also have shown to be associated with metabolic

and cardiovascular outcomes^{62,63}. In addition, to investigate the impact on the quantity and quality of social interactions several social variables were analysed, as these have been shown to affect CVD risk⁶⁴. Loneliness (UK Biobank variable identifier: 2020) was operationalised as a binary variable based on the question, “Do you often feel lonely?”, to which individuals answered “yes” (coded as 1) or “no” (coded as 0). The Ability to Confide (UK Biobank variable identifier: 2110) was also operationalised as a binary variable, based on the question, “How often are you able to confide in someone close to you?”. As per previous research⁶⁵, responses ranging from “almost daily” to “about once a month” were coded as “0”, and responses ranging from “once every few months” to “never” were coded as “1”. Social Contact Frequency was operationalised as a composite binary variable based on the questions, ‘Including yourself, how many people are living together in your household?’ (UK Biobank variable identifier: 709) and ‘How often do you visit friends or family or have them visit you?’ (UK Biobank variable identifier: 1031). Those who lived alone and who indicated that they either never visited or had no friends or family who visited were coded as “1”, and those who either did not live alone, or had friends who visited at least once a week were coded as “0” as done in previous research⁶⁶. Engagement in leisure and social activities (UK Biobank variable identifier: 6160) was converted into a binary variable, determined by the response to the question, “Which of the following do you attend once a week or more often? (you can select more than one)”, with the response options “sports club or gym”, “pub or social club”, “religious group”, “adult education class”, and “other group activity”. Individuals who reported habitual participation in at least one activity were coded as “0”, all others as “1”, as reported in previous literature⁶⁶.

Statistical analysis

All statistical analyses were done using R version 4.0.0 (2020-04-24)⁶⁷. To analyse the relationships between continuous variables we fitted linear regression models, controlling for sex, age, and age² and 10 top principal components from the variance-standardized

relationship matrix to account for population stratification. For dichotomous variables, we fitted logistic regression models, also controlling for sex, age, and age² and 10 top principal components from the variance-standardized relationship matrix. FDR correction across all tests was used to control for multiple testing. Sex was determined from genetic data. To analyse the relationships between individual phenotypes we also performed pairwise correlations between all the phenotypic variables. Complete linkage hierarchical clustering was subsequently performed on the resulting correlation matrix, to identify clusters of correlating variables. Analysis scripts to reproduce the data processing and analyses are available at <https://osf.io/gpdxm/>. In addition, due to the fact that PRSs calculated from any set of SNPs will have a non-zero effect, we compared the effects sizes of the various models against those of models using PRSs calculated from 100 random, unique gene-sets of equal size to assess the specificity of the results. These distributions were often not symmetrical, possibly due to associations between the analysed phenotype and the target phenotype for the PRS calculation.

Results

Associations between cardiovascular risk factor phenotypes

Pairwise correlation analyses revealed strong associations between BMI variables, trunk fat and whole-body fat, between grip strength and waist-to-hip ratio (Fig. 1, Supplementary table 1), and between the three dietary variables and between loneliness and the ability to confide. The hierarchical analysis found three main clusters of metabolic predictors—a BMI/body fat cluster, a dietary cluster, and a grip strength/waist-to-hip ratio cluster. All variables within clusters had statistically significant relationships (all p 's < 0.05, FDR corrected).

Bipolar disorder Oxytocin-specific polygenic risk scores vs CVD risk factors

No significant association was detected between BMI and BD PRS_{oxl}, BD PC1_{oxl}, (both linear models $p_{\text{fdr}} > .05$) while BD PC2_{oxl} was significantly negatively associated with BMI ($p_{\text{fdr}} = .026$; Supplementary tables 2-4; Fig. 2) and BMI calculated from impedanciometry ($p_{\text{fdr}} = .03$), with these results being in the lower end of effect sizes compared to the random gene-set PRS models (Fig. 3). Neither whole-body fat percentage nor trunk fat percentage, waist to hip ratio or grip strength showed significant associations with BD PRS_{oxl}, BD PC1_{oxl} or BD PC2_{oxl} (all $p_{\text{fdr}} > 0.05$). Of the dietary variables, total sugar intake was significantly negatively associated with BD PC2_{oxl} ($p_{\text{fdr}} \text{'s} < .001$) but not BD PRS_{oxl} or BD PC1_{oxl} (both $p_{\text{fdr}} > .05$) with an effect size at the lower 5% of the distribution of random gene-set PRS models and food weight was only significantly positively associated with BD PC1_{oxl} and BD PRS_{oxl} ($p_{\text{fdr}} < .001$), with effect sizes in the top 5% of the random PRS model distribution.

Logistic regressions of loneliness on BD PRS_{oxl}, BD PC1_{oxl}, and BD PC2_{oxl} showed no significant associations (all $p_{\text{fdr}} > .05$; Supplementary tables 5-7; fig. 4). Logistic regressions of ability to confide showed significant negative associations with BD PRS_{oxl} and BD PC1_{oxl} (both $p_{\text{fdr}} = .02$ and $p_{\text{fdr}} = .03$ respectively) but not BD PC2_{oxl} ($p_{\text{fdr}} > .5$), with effect sizes at the lower end of the random gene-set PRS model distribution. BD PRS_{oxl} and BD PC1_{oxl} scores showed significant positive association with participation in social activities (both $p_{\text{fdr}} = 0.035$), but the effects sizes were average compared to those of the random gene-set PRS model distribution. None of the polygenic score models with the presence of social contacts showed any significant association (all $p_{\text{fdr}} > 0.05$).

Schizophrenia Oxytocin-specific polygenic risk scores vs CVD risk factors

Linear models demonstrated a significant positive association of BMI, BMI calculated from impedanciometry and trunk fat percentage with SCZ PC2_{oxl} ($p_{\text{fdr}} < .005$), but not with SCZ PRS_{oxl}, SCZ PC1_{oxl} (both $p_{\text{fdr}} > .05$; Supplementary tables 2-4; fig. 2), with all effects in the top 5% of the random gene-set PRS model distributions (fig. 3). We also found no significant

association between both total body fat percentage and SCZ PRS_{ox}, SCZ PC1_{ox} and SCZ PC2_{ox} (all $p_{\text{fdr}} < .005$). Linear regressions of waist-to-hip ratio showed significant positive associations with SCZ PRS_{ox} and SCZ PC1_{ox} (both $p_{\text{fdr}} < .001$) but not with PRS_{ox} or PC2_{ox} ($p_{\text{fdr}} > .05$) with effect sizes in the top 5% of the random gene-set PRS model distribution (fig. 3). Significant positive associations were also found between grip strength and SCZ PRS_{ox}, SCZ PC1_{ox}, and negative with SCZ PC2_{ox} (all $p_{\text{fdr}} < .001$). None of the models of any dietary variable showed any significant associations with SCZ PRS_{ox}, SCZ PC1_{ox} or SCZ PC2_{ox} (all $p_{\text{fdr}} > .05$).

Logistic regressions of loneliness showed consistently significant positive associations with SCZ PRS_{ox}, SCZ PC1_{ox} (both p_{fdr} 's $< .001$; Supplementary tables 5-7; fig. 4) but not with SCZ PC2_{ox} ($p_{\text{fdr}} > .05$), though these significant effects were average within the random gene-set PRS model distribution. None of the other social variables showed any significant association with PRS_{ox}, SCZ PC1_{ox} or PC2_{ox} (all $p_{\text{fdr}} > .05$).

Type 2 Diabetes Mellitus Oxytocin-specific polygenic risk scores vs CVD risk factors

Linear models revealed a significant positive relationship between T2D PRS_{ox}, T2D PC1_{ox}, T2D PC2_{ox} and BMI (all p_{fdr} 's $< .001$; Supplementary tables 2-4; fig. 2) as well as BMI calculated from impedanciometry (all p_{fdr} 's $< .001$), with these effects in the top 10% of the random gene-set PRS model distribution (fig. 3). Models between T2D PRS_{ox}, T2D PC1_{ox} and whole-body fat percentage (both p_{fdr} 's $< .001$) and trunk fat percentage (both p_{fdr} 's $< .001$) showed significant positive associations, but these effects are average within the random gene-set PRS model distributions (fig. 3). We also found significant positive relationships in models between waist-to-hip ratio and T2D PRS_{ox}, T2D PC1_{ox} and T2D PC2_{ox} (all p_{fdr} 's $< .001$), with the effects of the T2D PRS_{ox} and T2D PC1_{ox} models in the top 5% of the random gene-set PRS model distribution. In addition, we found a negative association between grip strength and T2D PRS_{ox} and T2D PC1_{ox} (both p_{fdr} 's $< .001$), but not T2D PC2_{ox} ($p_{\text{fdr}} > .05$),

with effect sizes in the bottom 5% of the random gene-set PRS model distributions. Of the dietary variables, only the linear model between total caloric intake, T2D PC1_{oxl} showed significant negative associations (p_{fdr} 's = .01), with this effect size in the bottom 5% of the random gene-set PRS model distribution. Of the social variables, only the logistic regression for the ability to confide and T2D PRS_{oxl}, showed significant positive associations (p_{fdr} = .003), with an effect size at the very top of the random gene-set PRS model distribution (fig. 3).

Discussion

The present results derived from a sample of just under half a million participants suggest that the oxytocin system has pleiotropic effects on both social and metabolic phenotypes¹⁶ by providing evidence for the involvement of the oxytocin signalling pathway in the shared genetic liability of schizophrenia, bipolar disorder, T2D and several phenotypes linked with CVD and T2D risk. While the effect sizes generated by these analyses were relatively small, they were comparable with those of other reports on polygenic risk scores^{68,69}, as well as often showing specificity to the oxytocin pathway when compared to models with random gene-set PRSs (fig. 4).

The PRS_{oxl} and PC-PRS_{oxl} were used as proxies for the oxytocin-pathway-specific liability for schizophrenia, bipolar disorder, and type 2 diabetes mellitus to investigate the genetic association with CVD risk factors. While overall PRSs that combine the effect of all the SNPs associated with a specific phenotype (e.g., schizophrenia) may be better for predicting overall associations, pathway-specific PRS can be more suitable for investigating specific components of the underlying pathology⁵², and have been used successfully in investigating psychotic disorders⁷⁰. This is particularly relevant in the realm of oxytocin research, where studies have historically used candidate gene and single SNP approaches^{71–}

In the initial pairwise correlation and clustering analysis, we identified three main clusters of metabolic predictors: BMI, trunk fat, and total body fat (body fat cluster); energy intake, sugar intake and food weight (eating habits cluster), and grip strength and waist-to-hip ratio (strength/WH ratio cluster). The body fat cluster showed a positive association with the oxytocin-specific PRS and the first PC-PRS_{oxyt} for T2D and the second PC-PRS_{oxyt} for SCZ, and a negative association with the second PC-PRS_{oxyt} for BD. The food intake cluster points to an involvement of the oxytocin pathway in the regulation of caloric intake, appetite and preference for sweet food, consistent with previous reports¹⁸. While the relationship between grip strength and waist-to-hip ratio (grip strength/WH ratio cluster) is less expected than the other clusters, these highly-related markers both have prognostic value for cardiovascular events and mortality^{59,74}.

Four variables were included to investigate the role of oxytocin pathway variants on social behaviour: Loneliness, the ability to confide, social contacts, and social activity. Loneliness and the ability to confide represent the subjective dissatisfaction with one's relationships and were significantly associated with the oxytocin pathway PRSs. These associations with the oxytocin pathway are in line with previous findings on emotional withdrawal in individuals with schizophrenia³² and on the symptomatology of individuals with bipolar disorder^{75,76}. While the level of social contacts was strongly linked with loneliness, it was not associated with most of the oxytocin-specific PRSs. In other words, although many participants in the present sample reported that they had very little social contact, this was not necessarily *distressing* for all these individuals, and oxytocin pathway variants were found to be associated with reported dissatisfaction with the quantity or quality of social contact. Associations between participation in social activities and oxytocin PRS scores was present for those pertaining to schizophrenia and bipolar disorder, suggesting that oxytocin pathway variants are associated with social isolation in severe mental illness.

It has recently been proposed that the primary purpose of the oxytocin signalling system is the support of allostasis, which is the process of maintaining stability in changing

environments²⁴. This is a departure from existing theories of oxytocin's purpose that focus on its social effects⁷⁷, however, it better reflects the emerging literature demonstrating its non-social effects and its evolutionary history²⁴. Organism survival depends on efficient energy regulation, which is facilitated by adjusting behaviours based on current and predicted environmental conditions. For humans, an important element of predicting future environmental conditions is understanding the thoughts and intentions of other people. For example, the distinction between facial expression cues that can reveal whether someone else is going to help or harm can be very subtle. Oxytocin-like peptides first emerged around 600 million years ago⁷⁸, facilitating muscle contraction, locomotion, and food-related learning⁷⁹ in the service of energy regulation and reproduction. The Allostatic theory of Oxytocin suggests that oxytocin signalling adapted over time to include the coordination of social behaviour to help support energy regulation processes, which is consistent with the present results regarding energy intake and body composition.

There has been a growing interest from biobehavioural science in oxytocin's role in behaviour¹⁷. However, the relationship between oxytocin's behavioural and physical effects, and the implications for its behavioural effects are seldom discussed¹⁷. The present study adds to increasing genetic evidence that the oxytocin system is associated with a broad range of mental and physical effects⁸⁰, and that the function of the oxytocin system has a pleiotropic influence on both these groups of phenotypes. It is conceivable that part of this observed genetic pleiotropy could be explained by population stratification and non-random sample selection in the original GWAS', for instance, due to varying exclusion criteria related to somatic conditions for patients and healthy controls. Another potential limitation is the lack of a sex-disaggregated PRS score that would better account for sex-specific confounders⁸¹, which is relevant for oxytocin research¹⁷. In addition, this methodology cannot explain the biological mechanisms that underly the relationships found, as PRSs assume an additive effect of individual risk alleles and do not model higher order relationships between risk variants.

Altogether, the shared effect of oxytocin system dysfunction helps provide a better understanding of why social and metabolic dysfunction often co-occurs in severe mental illnesses. Future investigations examining the effects of long-term effects of intranasal oxytocin administration on behavior and cognition in severe mental illnesses, such as schizophrenia, should also explore oxytocin's effects on metabolic measures in tandem.

Acknowledgements

This work was supported the Novo Nordisk Foundation (NFF16OC0019856) and the Research Council of Norway (301767). Thank you to Michel Nivard for valuable feedback on a previous version of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Table 1. Anthropometric and cardiovascular variables

Variable	Observation count	UK Biobank code(s)
BMI (kg/m ²)	485,323	21001
BMI estimated by impedance (kg/m ²)	478,550	23104
Waist to hip ratio	486,124	48; 49
Grip strength (kg)	484,084	46; 47
Whole body fat percentage	478,285	23099
Trunk fat percentage	478,235	23127
Total daily energy intake (kJ)	206,524	100002
Total daily sugar intake (g)	206,524	100008
Total daily food weight (g)	206,524	100001
Loneliness	478,140	2020
Ability to confide	469,417	2110
Social contacts	499,373	709; 1031
Participation in social activities	497,030	6160

Figure 1. Associations between continuous phenotypes. Hierarchical analysis revealed three main clusters of associations: a BMI/body fat cluster, a dietary cluster, and a grip strength/waist-to-hip ratio cluster. All variables within clusters were significantly associated with each other (all p 's < 0.05, FDR corrected).

Figure 2. Effect sizes and confidence intervals for the linear models of continuous variables. Different colours correspond to the three different PRS_{oxy}'s and PC-PRS_{oxy}'s. BD = Bipolar Disorder, SCZ = Schizophrenia, T2D = Type 2 Diabetes Mellitus, PRS_{oxy} = Polygenic risk score for the oxytocin pathway, PC1 = First principal component, PC2 = Second principal component.

Figure 3. Distribution plots of the effect sizes of the PRS_{ox}t and PC-PRS_{ox}t models and models from PRSs calculated from 100 random genesets of equal size. We found that a number of the statistically significant effects are specific to the oxytocin pathway and not due to the random association of the SNP in the gene-set with the chosen phenotypes: Schizophrenia, bipolar disorder or type 2 diabetes. PRS = Polygenic risk score, PC1 = First principal component, PC2 = Second principal component.

Figure 4. Effect sizes and confidence intervals for the logistic regression models of the dichotomous variables. The different colours correspond to the three different PRS_{oxyt}'s and PC-PRS_{oxyt}'s. BD = Bipolar Disorder, SCZ = Schizophrenia, T2D = Type 2 Diabetes Mellitus, PRS_{oxyt} = Polygenic risk score for the oxytocin pathway, PC1 = First principal component, PC2 = Second principal component.

References

1. Chang, C.-K. *et al.* Life Expectancy at Birth for People with Serious Mental Illness and Other Major Disorders from a Secondary Mental Health Care Case Register in London. *PLOS ONE* **6**, e19590 (2011).
2. Weye, N. *et al.* Association of Specific Mental Disorders With Premature Mortality in the Danish Population Using Alternative Measurement Methods. *JAMA Netw. Open* **3**, e206646 (2020).
3. Gladigau, E. L., Fazio, T. N., Hannam, J. P., Dawson, L. M. & Jones, S. G. Increased cardiovascular risk in patients with severe mental illness. *Intern. Med. J.* **44**, 65–69 (2014).
4. Vancampfort, D. *et al.* Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry Off. J. World Psychiatr. Assoc. WPA* **14**, 339–47 (2015).
5. Alberti, K. G. M. M., Zimmet, P. & Shaw, J. The metabolic syndrome - A new worldwide definition. *Lancet* **366**, 1059–1062 (2005).
6. Birkenaes, A. B. *et al.* The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. *J. Clin. Psychiatry* **68**, 917–23 (2007).
7. Mitchell, A. J. *et al.* Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders-a systematic review and meta-analysis. *Schizophr. Bull.* **39**, 306–318 (2013).
8. Daumit, G. L. *et al.* Physical Activity Patterns in Adults With Severe Mental Illness. *J. Nerv. Ment. Dis.* **193**, 641–646 (2005).
9. Fontaine, K. R. *et al.* Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. *Psychiatry Res.* **101**, 277–288 (2001).
10. Venkatasubramanian, G. *et al.* Insulin and insulin-like growth factor-1 abnormalities in antipsychotic-naïve schizophrenia. *Am. J. Psychiatry* **164**, 1557–1560 (2007).
11. Raphael, T. & Parsons, J. P. Blood sugar studies in dementia praecox and manic depressive insanity. *Arch. Neurol. Psychiatry* **5**, 687 (1921).
12. Fernandez-Egea, E. *et al.* Glucose abnormalities in the siblings of people with schizophrenia. *Schizophr. Res.* **103**, 110–3 (2008).
13. Andreassen, O. A. *et al.* Identifying common genetic variants in blood pressure due to polygenic pleiotropy with associated phenotypes. *Hypertens. Dallas Tex* **63**, 819–26 (2014).
14. Morgan, V. A. *et al.* Responding to challenges for people with psychotic illness: Updated evidence from the Survey of High Impact Psychosis. *Aust. N. Z. J. Psychiatry* **51**, 124–140 (2017).
15. Holt-Lunstad, J. & Smith, T. B. Loneliness and social isolation as risk factors for CVD: implications for evidence-based patient care and scientific inquiry. *Heart Br. Card. Soc.* **102**, 987–9 (2016).
16. Quintana, D. S., Dieset, I., Elvsåshagen, T., Westlye, L. T. & Andreassen, O. A. Oxytocin system dysfunction as a common mechanism underlying metabolic syndrome and psychiatric symptoms in schizophrenia and bipolar disorders. *Front. Neuroendocrinol.* **45**, 1–10 (2017).

17. Winterton, A., Westlye, L. T., Steen, N. E., Andreassen, O. A. & Quintana, D. S. Improving the precision of intranasal oxytocin research. *Nat. Hum. Behav.* 1–10 (2020) doi:10.1038/s41562-020-00996-4.
18. Leng, G. & Sabatier, N. Oxytocin – The Sweet Hormone? *Trends Endocrinol. Metab.* **28**, 365–376 (2017).
19. Alvares, G. A., Quintana, D. S. & Whitehouse, A. J. O. Beyond the hype and hope: Critical considerations for intranasal oxytocin research in autism spectrum disorder. *Autism Res.* **10**, 1–17 (2016).
20. Carter, C. S., Williams, J. R., Witt, D. M. & Insel, T. R. Oxytocin and Social Bonding. *Ann. N. Y. Acad. Sci.* **652**, 204–211 (1992).
21. Insel, T. R., Winslow, J. T., Wang, Z. & Young, L. J. Oxytocin, Vasopressin, and the Neuroendocrine Basis of Pair Bond Formation. in 215–224 (Springer, Boston, MA, 1998). doi:10.1007/978-1-4615-4871-3_28.
22. Carter, C. S. Oxytocin and sexual behavior. *Neurosci. Biobehav. Rev.* **16**, 131–144 (1992).
23. Guastella, A. J. & MacLeod, C. A critical review of the influence of oxytocin nasal spray on social cognition in humans: Evidence and future directions. *Hormones and Behavior* vol. 61 410–418 (2012).
24. Quintana, D. S. & Guastella, A. J. An allostatic theory of oxytocin. *Trends Cogn. Sci.* (2020) doi:https://doi.org/10.1016/j.tics.2020.03.008.
25. Ott, V. *et al.* Oxytocin reduces reward-driven food intake in humans. *Diabetes* **62**, 3418–3425 (2013).
26. Lawson, E. A. *et al.* Oxytocin reduces caloric intake in men. *Obes. Silver Spring Md* **23**, 950–6 (2015).
27. Blevins, J. E. *et al.* Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **308**, R431-8 (2015).
28. Gutkowska, J., Jankowski, M., Mukaddam-Daher, S. & McCann, S. M. Oxytocin is a cardiovascular hormone. *Braz. J. Med. Biol. Res. Rev. Bras. Pesqui. Medicas E Biol.* **33**, 625–33 (2000).
29. Gimpl, G., Farenholtz, F., Fahrenholz, F. & Gene, C. The oxytocin receptor system: Structure, function and regulation. *Physiol. Rev.* **81**, 629–683 (2001).
30. Petersson, M. Cardiovascular effects of oxytocin. in *Progress in Brain Research* vol. 139 281–288 (Elsevier, 2002).
31. Kemp, A. H. *et al.* Oxytocin Increases Heart Rate Variability in Humans at Rest: Implications for Social Approach-Related Motivation and Capacity for Social Engagement. *PLoS ONE* **7**, e44014 (2012).
32. Haram, M. *et al.* Association between Genetic Variation in the Oxytocin Receptor Gene and Emotional Withdrawal, but not between Oxytocin Pathway Genes and Diagnosis in Psychotic Disorders. *Front. Hum. Neurosci.* **9**, (2015).

33. Montag, C. *et al.* Oxytocin and oxytocin receptor gene polymorphisms and risk for schizophrenia: A case–control study. *World J. Biol. Psychiatry* **14**, 500–508 (2013).
34. Shilling, P. D. & Feifel, D. Potential of Oxytocin in the Treatment of Schizophrenia. *CNS Drugs* **30**, 193–208 (2016).
35. Lee, M. R. *et al.* Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: results from a randomized double blind placebo controlled pilot study. *Schizophr. Res.* **145**, 110–5 (2013).
36. Cacciotti-Saija, C. *et al.* A Double-Blind Randomized Controlled Trial of Oxytocin Nasal Spray and Social Cognition Training for Young People With Early Psychosis. *Schizophr. Bull.* **41**, 483–493 (2015).
37. Jarskog, L. F. *et al.* A 12-week randomized controlled trial of twice-daily intranasal oxytocin for social cognitive deficits in people with schizophrenia. *Schizophr. Res.* **185**, 88–95 (2017).
38. Declerck, C. H., Boone, C., Pauwels, L., Vogt, B. & Fehr, E. A registered replication study on oxytocin and trust. *Nat. Hum. Behav.* **4**, 646–655 (2020).
39. Walum, H., Waldman, I. D. & Young, L. J. Statistical and Methodological Considerations for the Interpretation of Intranasal Oxytocin Studies. *Biol. Psychiatry* **79**, 251–257 (2016).
40. Quintana, D. S., Guastella, A. J., Westlye, L. T. & Andreassen, O. A. The promise and pitfalls of intranasally administering psychopharmacological agents for the treatment of psychiatric disorders. *Molecular Psychiatry* vol. 21 29–38 (2016).
41. Feldman, R., Feldman, R., Monakhov, M., Pratt, M. & Ebstein, R. P. Oxytocin Pathway Genes : Evolutionary Ancient System Impacting on Human Affiliation , Review Oxytocin Pathway Genes : Evolutionary Ancient System Impacting on Human Af fi liation ,. *Biol. Psychiatry* 1–11 (2015) doi:10.1016/j.biopsych.2015.08.008.
42. Harden, K. P. “Reports of My Death Were Greatly Exaggerated”: Behavior Genetics in the Postgenomic Era. *Annu. Rev. Psychol.* **72**, annurev-psych-052220-103822 (2021).
43. Harden, K. P. & Koellinger, P. D. Using genetics for social science. *Nat. Hum. Behav.* **4**, 567–576 (2020).
44. Sudlow, C. *et al.* UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Med.* **12**, e1001779 (2015).
45. UK Biobank. UK Biobank: Protocol for a large-scale prospective epidemiological resource. **06**, 1–112 (2007).
46. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
47. Kamburov, A., Stelzl, U., Lehrach, H. & Herwig, R. The ConsensusPathDB interaction database: 2013 update. *Nucleic Acids Res.* **41**, D793–D800 (2013).
48. Durinck, S., Spellman, P. T., Birney, E. & Huber, W. Mapping identifiers for the integration of genomic datasets with the R/Bioconductor package biomaRt. *Nat. Protoc.* **4**, 1184–1191 (2009).
49. Lesurf, R. *et al.* ORegAnno 3.0: a community-driven resource for curated regulatory annotation. *Nucleic Acids Res.* **44**, D126–D132 (2016).

50. Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
51. Euesden, J., Lewis, C. M. & O'Reilly, P. F. PRSice: Polygenic Risk Score software. *Bioinformatics* **31**, 1466–1468 (2015).
52. Darst, B. F. *et al.* Pathway-specific polygenic risk scores as predictors of β -amyloid deposition and cognitive function in a sample at increased risk for Alzheimer's disease. *J. Alzheimers Dis. JAD* **55**, 473–484 (2017).
53. Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke, S., Walters, J. T. & O'Donovan, M. C. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. *medRxiv* 2020.09.12.20192922 (2020) doi:10.1101/2020.09.12.20192922.
54. Stahl, E. A. *et al.* Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat. Genet.* **51**, 793–803 (2019).
55. Morris, A. P. *et al.* Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* **44**, 981–990 (2012).
56. Coombes, B. J., Ploner, A., Bergen, S. E. & Biernacka, J. M. A principal component approach to improve association testing with polygenic risk scores. *Genet. Epidemiol.* **44**, 676–686 (2020).
57. Alnæs, D. *et al.* Brain Heterogeneity in Schizophrenia and Its Association With Polygenic Risk. *JAMA Psychiatry* **76**, 739 (2019).
58. de Lange, A.-M. G. *et al.* Population-based neuroimaging reveals traces of childbirth in the maternal brain. *Proc. Natl. Acad. Sci. U. S. A.* **116**, 22341–22346 (2019).
59. Leong, D. P. *et al.* Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *The Lancet* **386**, 266–273 (2015).
60. Lawman, H. G. *et al.* Associations of Relative Handgrip Strength and Cardiovascular Disease Biomarkers in U.S. Adults, 2011–2012. *Am. J. Prev. Med.* **50**, 677–683 (2016).
61. Kim, Y. *et al.* Independent and joint associations of grip strength and adiposity with all-cause and cardiovascular disease mortality in 403,199 adults: the UK Biobank study. *Am. J. Clin. Nutr.* **106**, 773–782 (2017).
62. Dalton, M. *et al.* Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. *J Intern Med* **254**, 555–563 (2003).
63. Franssen, F. M. E. *et al.* New Reference Values for Body Composition by Bioelectrical Impedance Analysis in the General Population: Results From the UK Biobank. *J. Am. Med. Dir. Assoc.* **15**, 448.e1–448.e6 (2014).
64. Valtorta, N. K., Kanaan, M., Gilbody, S., Ronzi, S. & Hanratty, B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: Systematic review and meta-analysis of longitudinal observational studies. *Heart* **102**, 1009–1016 (2016).
65. Elovainio, M. *et al.* Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. *Lancet Public Health* **2**, e260–e266 (2017).

66. Day, F. R., Ong, K. K. & Perry, J. R. B. Elucidating the genetic basis of social interaction and isolation. *Nat. Commun.* **9**, 2457 (2018).
67. R Core Team. *R: A Language and Environment for Statistical Computing*. (R Foundation for Statistical Computing, 2020).
68. Begum, F., Ghosh, D., Tseng, G. C. & Feingold, E. Comprehensive literature review and statistical considerations for GWAS meta-analysis. *Nucleic Acids Res.* **40**, 3777–3784 (2012).
69. Dudbridge, F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet.* **9**, e1003348 (2013).
70. Holland, J. F. *et al.* Effects of complement gene-set polygenic risk score on brain volume and cortical measures in patients with psychotic disorders and healthy controls. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **183**, 445–453 (2020).
71. Poore, H. E. & Waldman, I. D. The Association of Oxytocin Receptor Gene (OXTR) Polymorphisms Antisocial Behavior: A Meta-analysis. *Behav. Genet.* **50**, 161–173 (2020).
72. Baribeau, D. A. *et al.* Oxytocin Receptor Polymorphisms are Differentially Associated with Social Abilities across Neurodevelopmental Disorders. *Sci. Rep.* **7**, 11618 (2017).
73. Uzefovsky, F. *et al.* The oxytocin receptor gene predicts brain activity during an emotion recognition task in autism. *Mol. Autism* **10**, 12 (2019).
74. de Koning, L., Merchant, A. T., Pogue, J. & Anand, S. S. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur. Heart J.* **28**, 850–856 (2007).
75. Turan, T., Uysal, C., Asdemir, A. & Kılıç, E. May oxytocin be a trait marker for bipolar disorder? *Psychoneuroendocrinology* **38**, 2890–2896 (2013).
76. Wei, S.-Y. *et al.* Dysregulation of oxytocin and dopamine in the corticostriatal circuitry in bipolar II disorder. *Transl. Psychiatry* **10**, 281 (2020).
77. Shamay-Tsoory, S. G. & Abu-Akel, A. The social salience hypothesis of oxytocin. *Biol. Psychiatry* **79**, 194–202 (2016).
78. Gwee, P.-C., Tay, B.-H., Brenner, S. & Venkatesh, B. Characterization of the neurohypophysial hormone gene loci in elephant shark and the Japanese lamprey: origin of the vertebrate neurohypophysial hormone genes. *BMC Evol. Biol.* **9**, 47 (2009).
79. Beets, I. *et al.* Vasopressin/oxytocin-related signaling regulates gustatory associative learning in *C. elegans*. *Science* **338**, 543–545 (2012).
80. Quintana, D. S. *et al.* Oxytocin pathway gene networks in the human brain. *Nat. Commun.* **10**, 668 (2019).
81. Flynn, E. *et al.* Sex-specific genetic effects across biomarkers. *Eur. J. Hum. Genet. EJHG* (2020) doi:10.1038/s41431-020-00712-w.