Reconsidering the reasons for heightened inflammation in major depressive disorder

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Abstract

Background: Increased circulating pro-inflammatory markers have repeatedly been associated with major depressive disorder (MDD). However, it remains unclear whether inflammation represents a causal mechanism for MDD, or whether the association is influenced by confounding factors such as body mass index (BMI).

Methods: To better understand this complex relationship, we generated polygenic risk scores (PRS) for MDD and BMI in a population cohort and attempted to isolate the impact these potential risk factors have on adulthood inflammation. Peripheral blood samples were collected as part of the South East London Community Health study, where we generated individualized PRS for MDD and BMI and quantified inflammatory markers using multiplex ELISA-based technology. We performed linear regressions to investigate the effects of PRS for MDD and BMI on inflammatory marker levels.

Results: Out of 35 inflammatory markers, we found a nominal effect of PRS for MDD on interleukin-10. We also found a significant positive effect of BMI on nine inflammatory markers, of which the two most strongly affected markers, interleukin-6 (IL-6) and C-reactive protein (CRP), were also nominally predicted by BMI PRS.

Limitations: The study utilized a cross-sectional design with a moderately sized sample.

Conclusions: Our findings suggest there may not be a shared genetic mechanism contributing to MDD and higher inflammatory marker levels. However, there may be shared genetic etiology between BMI and adulthood levels of CRP and IL-6. Therefore, polygenic risk scores for BMI may represent a useful indicator for heightened levels of inflammation in adulthood.

1. Introduction

The total number of people with major depressive disorder (MDD) exceeded 300 million globally in 2015 and the World Health Organization (WHO) currently states that MDD is the single largest contributor to global disability worldwide (Friedrich, 2017). The pathophysiology of MDD is not yet fully understood, although numerous causal mechanisms have recently been proposed, with some studies suggesting that MDD could manifest as a result of aberrant immune functioning in the body (Dantzer et al., 2008; Harrison et al., 2009). According to this hypothesis, over-activation of inflammatory pathways can lead to a systemic increase in peripheral immune modulators known as cytokines, which have been associated with psychiatric symptoms in both humans and animal models (Dantzer et al., 2008; McNally et al., 2008). This suggestion is corroborated by case-control studies demonstrating heightened inflammation amongst MDD patients (Osimo et al., 2020), and in particular, those in an active episode (Dahl et al., 2014) .

However, research investigating inflammation in the context of MDD is often confounded by a number of extraneous factors. For example, an increase in circulating pro-inflammatory cytokines has also been associated with increased body mass index (BMI), smoking and poor diet (Kantor et al., 2013; Lee et al., 2013; Opel et al., 2015). These factors are highly prevalent in the MDD population (Kilian et al., 2006) and their confounding effect was highlighted recently by our work revealing strong positive associations between BMI and interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor (TNF) levels, above-and-beyond the influence of MDD case control status or childhood maltreatment effects (Palmos et al., 2019; Powell et al., 2018). Several other studies have also shown that high BMI is associated with pro-inflammatory cytokine release and a state of chronic inflammation, which in turn could lead to symptoms of MDD and inflammatory-related diseases such as cardiovascular disease and arthritis (Anuradha et al., 2016; Borges et al., 2018; Rea et al., 2018). This association is likely due to the correlation between BMI and abdominal fat levels, and in particular, the level of white adipose tissue, which is known to exert a strong effect on hormone regulation and on the storage and release of pro-inflammatory cytokines (Makki et al., 2013). Therefore, it is possible that BMI is a mediating factor for increased inflammation in MDD and other inflammatory conditions, and further research into the differential effects of MDD and BMI on circulating inflammatory markers could inform a more targeted treatment for these conditions. For example, other fields have successfully demonstrated targeted anti-inflammatory treatments, which could be repurposed in psychiatry for patients with inflammatory subtypes of MDD (Durham et al., 2016).

When studying disease etiology, using genetic risk scores as a proxy for disease susceptibility in a healthy population is one way to overcome the effect of confounding factors common in clinical cohorts (Palmos et al., 2018). Genetic factors play a significant role in determining risk for MDD and adulthood BMI, with studies reporting heritability estimates of around 40–50% and 41–85% respectively (Feng, 2016; Lohoff, 2010). MDD and BMI are both considered to be highly polygenic, meaning that many risk variants of small effect size confer genetic risk. Individual variants may have little diagnostic value, but by using summary statistics taken from mega-GWASs such as the ones carried out by the psychiatric genomics consortium (PGC et al., 2017) or the genetic investigation of anthropometric traits consortium

(Locke et al., 2015), it is now possible to calculate polygenic risk scores (PRS) for MDD and BMI, for any given individual (Euesden et al., 2015; Mullins et al., 2016; Wray et al., 2018).

In summary, current research suggests that although inflammation is associated with MDD, BMI is a strong mediating factor for pro-inflammatory cytokine release and represents a potentially important confounder. To investigate this in more detail, we tested for a shared genetic etiology between MDD and inflammatory marker levels, and between BMI and inflammatory marker levels. We achieved this by testing the effect of polygenic risk scores for MDD and BMI on levels of 35 inflammatory markers in a largely disease-free population cohort. This allowed us to isolate the influence of genetic risk signals, without confounding factors often present in clinical sample sets, such as medication use, higher incidences of smoking, drug use, and various other factors known to be associated with MDD or obesity. Our results indicate a far more important role for genetic risk for BMI than for MDD in explaining levels of inflammatory markers in adulthood.

2. Methods

2.1. The Sample

Peripheral blood samples used in this study were collected by venipuncture as part of the South East London Community Health Study (Hatch et al., 2012). SELCoH is a population study in London, UK, investigating mental and physical health in the general population (Hatch et al., 2011). Participants have so far received detailed phenotypic assessments as part of three separate phases. The first phase was carried out to assess common mental and physical health disorders in South East London; the second phase examined the roles of social context and policy in shaping patterns of health inequalities; and the third phase included the collection of biological specimens including blood for DNA extraction and serum separation. After collection, serum was stored at -80°C until required. Information relating to age, BMI and smoking status was collected in conjunction with blood samples. Participants information can be found in Table 1.

<< Table 1 >>

2.2. Ethics

The SELCoH study received ethics approval from the King's College London research ethics committee, reference PNM/12/13-152. Participation all provided written informed consent to taking part in the study.

2.3. Inflammatory Marker Quantification

Upon use, serum was thawed at room temperature and 41 inflammatory markers were quantified simultaneously using multiplex ELISA-based technology provided by the Meso Scale Discovery V-PLEX Plus Human Biomarker 40-Plex kit, and a customized human duplex kit assaying brain-derived neurotrophic factor (BDNF) and interferon-alpha (IFN-α). Note however, that interleukin-8 (IL-8) is

repeated twice on the 40-plex array (IL-8 and IL-8(HA)) alongside two different standard curves, allowing for a very wide range of IL-8 levels to be detected. We only utilized data from IL-8 (not IL-8(HA)) as our samples were detectable specifically within the range of this standard curve (0.0700 – 498 pg/mL). The 41 captured antibodies are etched to the bottom of five 96-well plates, each capturing between 2 and 10 inflammatory markers. Seven-point standard curves were run in duplicate on each plate in order to calculate absolute pg/mL values for the 80 samples assayed per plate, and a no-template control was used to correct for background fluorescence. Plates were scanned on the Mesoscale Scale Discovery MESO Quickplex SQ 120 reader at the MRC SGDP Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London. Pilot studies revealed very high intra-plate ($r > 0.99$) and inter-plate ($r > 0.97$) correlations, suggesting single measurements were acceptably reliable using this methodology. Furthermore, known quantities within the standard curves used on each plate, correlated very highly with quantities predicted by fluorescence intensity ($r > 0.99$).

2.4. Genotyping & Quality Control (Target dataset)

10 mL of blood was collected from subjects in tubes containing EDTA (BD Vacutainer; BD, NJ, USA) and stored at -80°C. DNA was then extracted using a standard in-house protocol (Freeman et al., 2003) and stored at -80°C. DNA samples were sent to the Affymetrix Research Services Laboratory in Santa Clara, California, USA. Genotyping for SELCoH was assayed using the UK Biobank Axiom Array which comprises of 820,967 genetic markers (Affymetrix, California, United States). Genotype data was put through quality control measures as outlined previously (Coleman et al.), using PLINK v1.9 (Purcell et al., 2007), as described previously (Palmos et al., 2019).

2.5. Polygenic Risk Score Quantification

2.5.1.PRSice Software

Individualized Polygenic Risk Scores (PRS) within our sample were calculated using PRSice, a PRS quantification software (Euesden et al., 2015). The software uses summary results from previously performed, well-powered GWAS (the base dataset) to generate PRS in our sample, SELCoH (the target dataset). Briefly, PRSice works by first clumping SNPs in the genotype PLINK files corresponding to the target dataset and removing those in high linkage disequilibrium, as this can falsely inflate polygenic scores. Subsequently, within the target dataset the number of risk alleles at a particular SNP is multiplied by that SNP's effect size (established in the base dataset), and then all the SNP information is summed. Where previous work has already validated the optimal number of SNPs to include in a PRS, the user can define which SNPs to include based on a p-value threshold in the base GWAS. Alternatively, a user can include a phenotype file corresponding to their target dataset and PRSice can automatically determine the best combination of SNPs from across a range of p-value thresholds (P_T), to predict the phenotype of interest.

For MDD PRS analyses, we set a $P_T = 0.1$, as defined by the recent Psychiatric Genomics Consortium MDD GWAS (Wray et al., 2018), whereby we included all SNPs under this threshold from the base dataset, to calculate polygenic risk scores in our target dataset. For BMI PRS analyses, because BMI data was available from all participants as a continuous variable, we determined the optimal P_T within

the SELCoH sample itself. We adjusted BMI for sex, age and ethnicity and tested the best combination of SNPs (under different p-value thresholds), to predict BMI in our cohort, using BMI GWAS summary statistics from the GIANT Consortium (Locke et al., 2015). We tested six p-value thresholds in total (P_T = 0.05, P_T = 0.1, P_T = 0.2, P_T = 0.3, P_T = 0.4, P_T = 0.5), whilst covarying for seven population covariates (PCs), using PRSice.

2.5.2. Base Datasets

The MDD base dataset (GWAS summary statistics) was obtained from the Psychiatric Genomics Consortium (PGC), website (https://www.med.unc.edu/pgc/results-and-downloads/downloads) and represents the largest GWAS for MDD to-date, consisting of 130,664 MDD cases and 330,470 controls (Wray et al., 2018). The BMI base dataset was downloaded from the Genetic Investigation of Anthropomorphic Traits (GIANT) Consortium website (the specific file is labelled BMI.SNPadjSMK) (Locke et al., 2015).

2.6. Statistical Analysis

2.6.1. Data Processing

Standard curves were used to determine absolute quantities (pg/mL) of each inflammatory marker. Absolute quantities (pg/mL) were then log-transformed to allow for parametric analyses. Subsequently, data points were removed if they exceeded +/- 2 standard deviations from the mean. We also excluded inflammatory markers where greater than 30% of the data was missing, leaving 35 inflammatory markers (Powell et al., 2020).

2.6.2. Major Depressive Disorder Analyses

To test the association between genetic risk for MDD and inflammatory marker levels, we performed linear regressions with log-protein levels as the dependent variable and a PRS for MDD as the independent variable, alongside ethnicity, smoking, plate/batch effects, gender, age, BMI and seven PCs as covariates. Multiple testing correction was performed using the Bonferroni method. Given a sample size of 406, and an $\alpha = 0.0014$ (0.05 / 35), we had 80% power to detect medium effect sizes $\rho > 0.2$ in our study.

2.6.3. Body Mass Index Analyses

First, we tested whether BMI correlated with inflammatory marker levels. Log-protein level was set as the dependent variable and BMI was set as the independent variable, with gender, age, ethnicity, smoking, plate/batch effects, and seven PCs as covariates. As above, we had 80% power to detect medium effect sizes in our sample of $\rho > 0.2$. Next, for those markers significantly affected by BMI, we determined if BMI PRS was also associated with levels of inflammatory markers by performing the same regression, but instead of BMI as the independent variable we included PRS for BMI. Multiple testing correction was performed using the Bonferroni method.

2.6.4. Sensitivity Analyses

We performed additional sensitivity analyses to verify the validity of our results. Given that inflammation has been associated with depression and some individuals in our sample had self-reported depressive symptoms, we first ran the same models as above with the inclusion of depression case/control status and depression severity at the time of blood collection as covariates, for any significant associations. Second, since BMI has previously been associated with depression risk, we ran a binary logistic regression with PRS for BMI as the independent variable and depression case/control (0/1) status as the dependent variable to test whether the genes responsible for BMI also predict depression diagnosis in our sample. Finally, for IL-6 and CRP, we ran the same model as above and individually tested for the potential mediating/confounding effect of physical illness (type-2 diabetes, arthritis, cardiovascular disease, stroke, high blood pressure and cancer), socioeconomic factors (employment status, educational attainment level) and antidepressant use, all of which were available within the SELCoH study.

3. Results

3.1. The effect of a polygenic risk for MDD on inflammatory marker levels

The first part of our regression analyses investigated the effect of PRS for MDD on inflammatory marker levels. Our findings revealed that higher polygenic risk for MDD correlates with higher IL-10 levels (β = 0.393, P = 0.016, R^2 = 0.02); this finding did not survive multiple testing correction, see Figure 1. No other inflammatory markers were found to be significant. See S1 in Supplementary Materials for a full table of results.

<<<Figure 1>>>

3.2. The effect of a polygenic risk for BMI on inflammatory marker levels

To narrow down which inflammatory markers should be the focus of our BMI PRS analyses, we first investigated the main effect of raw BMI scores on inflammatory marker levels. 15 inflammatory markers showed a significant association; nine of which survived multiple testing correction ($P < 0.0014$), see Figure 2(a). The optimal PRS for predicting BMI in SELCoH was defined by SNPs under $P_T = 0.2$ from the GIANT GWAS (N_{SNPs} = 24,507, $R^2 = 0.063$, $P = 3.364 \times 10^{-7}$). We then outputted individualized PRS for BMI and tested whether the inflammatory makers significantly affected by BMI also correlated with PRS for higher BMI. Our results showed that PRS for higher BMI is positively associated with three inflammatory markers, including Macrophage Inflammatory Protein (MIP)-1β (β = 0.228, P = 0.047, R^2 = 0.01), IL-6 (β = 0.302, P = 0.018, R^2 = 0.02) and CRP (β = 0.285, P = 0.018, R^2 = 0.01), see Figure 2(b). These findings did not survive multiple testing correction (i.e. $p > 0.006$). See S2 in Supplementary Materials for a full table of results.

<<<Figure 2>>>

3.3. Sensitivity analyses

The PRS for BMI did not significantly predict depression case/control status in a binary logistic regression model ($P > 0.05$), suggesting that increased IL-6 and CRP levels via genetic risk factors for BMI are independent of MDD diagnosis. In addition, we did not find a mediating/confounding effect of depression severity, physical illness, socioeconomic status or antidepressant use on CRP or IL-6 ($P > 0.05$), suggesting that PRS for BMI is exerting an independent effect on CRP and IL-6 levels. Finally, we did not find a mediating/confounding effect of depression severity, socioeconomic status or antidepressant use on IL-6. We did observe a nominally significant effect of arthritis and stroke history on IL-6 levels ($P < 0.05$), though these effects were independent of BMI, which remained significantly associated with IL-6 ($P < 0.001$).

4. Discussion

The first aim of our study was to investigate whether genetic risk for MDD was associated with higher levels of circulating pro-inflammatory cytokines. Given that numerous studies have reported BMI as a major confounding factor when studying inflammation (Kantor et al., 2013; Palmos et al., 2019), our second aim was to investigate whether a PRS for BMI was associated with pro-inflammatory cytokine levels. Our findings revealed nominal effects of genetic risk for MDD on IL-10 levels, but no effect on the levels of pro-inflammatory markers classically associated with MDD, such as IL-6 and CRP. We did however find that both high BMI and a genetic risk for high BMI were associated with higher levels of CRP and IL-6.

It is surprising that a genetic risk for MDD is not associated with adult levels of inflammatory markers, given increased inflammation has been reported as a risk factor for developing MDD (Smith et al., 2018), and non-human animal studies indicate a causal effect of increased inflammation on depression-like phenotypes (O'Connor et al., 2009). A lack of significant associations in our study could relate to the fact that BMI (as well as other factors) can have a very strong influence of inflammatory marker levels in clinical sample sets, especially CRP and IL-6 (Powell et al., 2018). Indeed, BMI has been shown to have a far stronger effect on inflammatory marker levels than MDD case/control status (Palmos et al., 2019; Shelton et al., 2015), or in our case, than the genetic risk for MDD. This prompted us to study the effects of BMI on inflammatory marker levels, and to test whether there is shared genetic etiology between BMI and inflammatory marker levels.

We found strong effects of BMI on levels of two pro-inflammatory modulators commonly associated with MDD (among other disease states), IL-6 and CRP (Khandaker et al., 2014; Smith et al., 2018; Valkanova et al., 2013). This effect was also mimicked at the genetic level, whereby PRS for higher BMI was nominally associated with higher levels of these markers. Studies have previously shown that high BMI and larger abdominal adiposity is associated with increased circulating levels of IL-6 and CRP (Khaodhiar et al., 2004; Rexrode et al., 2003), and that IL-6 and CRP gene polymorphisms are

associated with obesity (Todendi et al., 2015); but to our knowledge, this study is one of the first to demonstrate a similar effect using BMI polygenic risk scores as predictors. Mechanistically, it is likely that the increased levels of these inflammatory markers are due to an increase in adipose tissue in the body, which is supported by studies investigating adipose tissue as an endocrine organ and a regulator of inflammation (Ahima et al., 2000; Coppack, 2001; Juge-Aubry et al., 2005). Given that PRS can be applied to people from a young age, our results suggest that PRS for BMI could represent a useful way of identifying children at risk of increased adulthood inflammation and subsequent inflammatory related conditions. In addition, these findings highlight the importance of studying BMI in the context of MDD treatment, given that several studies have suggested that a reduction in BMI alone is associated with a decrease in inflammation and that this decrease may lead to subsequent reduction in depression symptoms, providing a valuable tool for clinical use (Miller et al., 2017; Powell et al., 2013; Shelton et al., 2015; Shelton and Miller, 2011).

It is important to note that our study has a number of limitations. First, the study is of cross-sectional design, meaning that we were unable to capture longitudinal changes in inflammatory marker levels. It would be important to test how the penetrance of the PRS change over time, and whether the PRS for MDD have stronger effects on inflammatory marker levels during development, or in conjunction with environmental stress. Second, it's possible that a relatively rare 'inflammatory subtype' of depression exists which is distinct from the more common causes of depression assayed in large GWAS (Milaneschi et al., 2016). For instance, a recent study suggests that atypical depression with neurovegetative symptoms may represent a subtype of depression with an inflammatory component (Badini et al., 2020). Furthermore, it is well established that a high proportion of hepatitis sufferers experience depression related to IFN-α treatment (Lotrich, 2009), and so we cannot rule out a causal role for inflammation in rarer subtypes of MDD not captured by our PRS. Though, our results suggest a major factor contributing to higher inflammation amongst the majority of MDD patients might be BMI. This is also supported by meta-analyses which reveal that the effect size denoting the association between IL-6 levels and MDD is five times higher when combining results from studies where BMI was not adjusted (Howren et al., 2009). Third, the PRS for BMI may be inherently better at predicting inflammatory marker expression compared to PRS for MDD because BMI is more heritable, and the corresponding PRS explains more variance. Consequently, larger sample sets may allow us to detect more subtle effects exerted by the PRS for MDD, which is not possible in this sample. Fourth, although BMI is a commonly used measure, recent studies suggest waist-to-hip ratios, or dietary indexes in conjunction with BMI can provide more accurate clinical utility (Kant and Graubard, 2005; Lam et al., 2015). These measures may have even greater relevance to inflammatory cytokine levels and should be considered in future studies. Finally, there may be other factors affecting inflammatory marker levels which we were unable to account for in our study, including seasonality (Ter Horst et al., 2016), time of day the blood was collected (Nakao, 2014) and effects of menstruation (O'Brien et al., 2007), which could have increased heterogeneity and lowered our power to detect genetic effects.

Immune modulators such as pro-inflammatory cytokines are strongly associated with an increased risk of psychiatric disorders such as MDD, as well as inflammatory conditions such as cardiovascular

disease (Dantzer et al., 2008; McNally et al., 2008 2019; Williams et al., 2019). Nevertheless, our study is the first to demonstrate that genetic risk for MDD may not be responsible for increased inflammatory marker levels in adulthood, rather a genetic risk for BMI may be associated with adulthood levels of inflammatory markers instead. These findings suggest that genetic risk scores for BMI may be useful in identifying individuals (including individuals with MDD), at risk for inflammatory-related conditions, and allow for early intervention. Future replication in larger longitudinal samples are now needed to assess the dynamic relationship between MDD, BMI and inflammation across the lifecourse, and to discern the temporal ordering of effect.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the submission folder.

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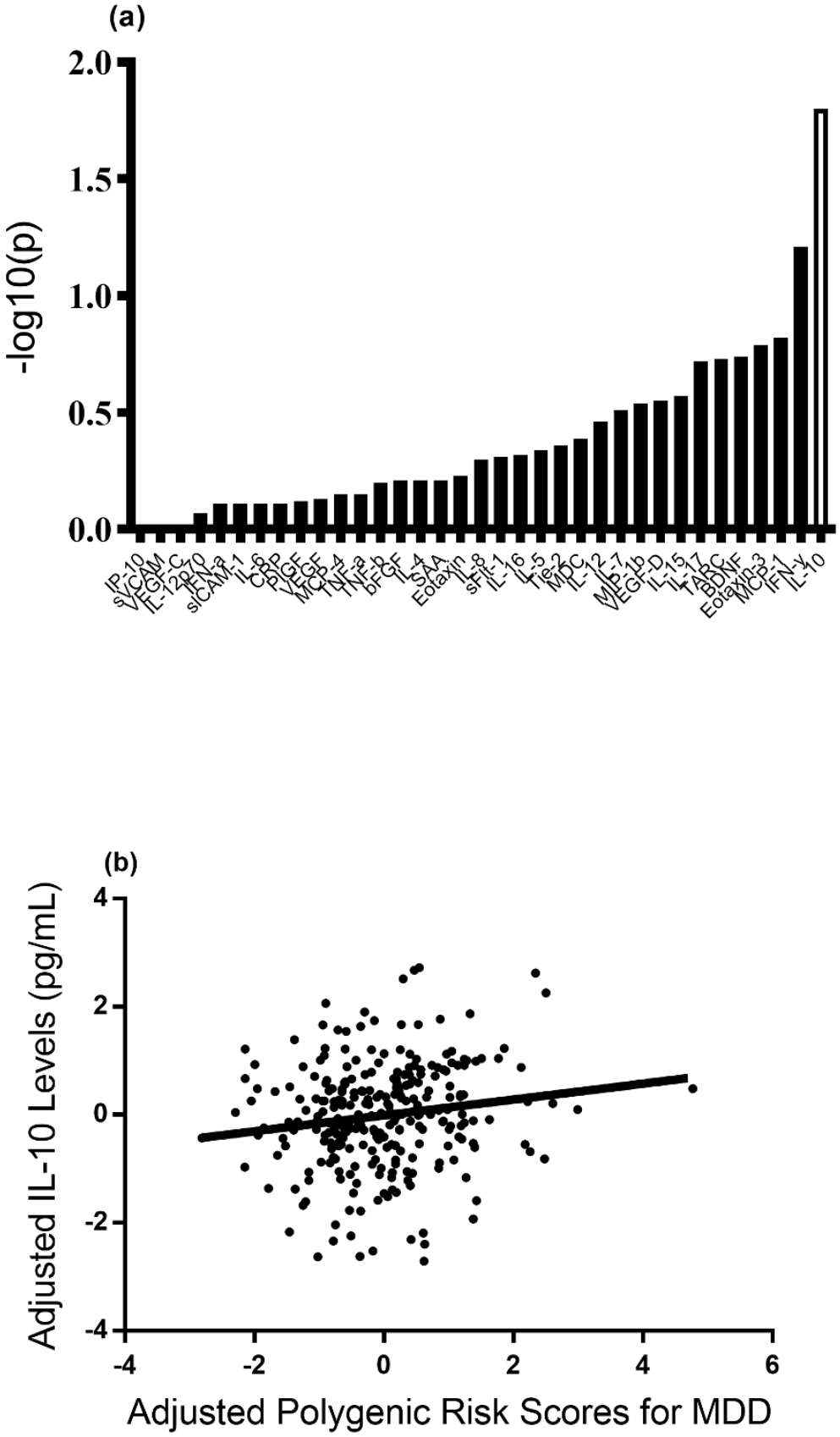
Figure & Table Legends

Table 1: Participant characteristics in the SELCoH sample.

Figure 1: The association between polygenic risk scores for MDD and inflammatory markers. This figure summarizes the linear associations between polygenic risk scores for MDD and 35 inflammatory markers. (a) A bar chart showing individual results from linear model with each inflammatory marker displayed on the x-axis and the negative log-transformed p-value for each inflammatory marker displayed on the y-axis. Nominally significant associations are represented by a white bar. (b) A graphical representation of the nominally significant association between polygenic risk scores for MDD and IL-10. Polygenic risk scores are displayed on the x-axis (adjusted for seven PCs) and IL-10 levels are displayed on the y-axis (adjusted for age, sex, gender, ethnicity, BMI and smoking status). The black line represented a line of best fit.

Figure 2: The association between BMI, polygenic risk scores for BMI and inflammatory markers. This figure summarizes the linear associations between BMI, polygenic risk scores for BMI and 35 inflammatory markers. (a) A bar chart showing individual results from linear models with BMI as the predictor, with each inflammatory marker displayed on the x-axis and log-transformed p-value for each inflammatory marker displayed on the y-axis. Nominally significant associations are represented by a white bar and the Bonferroni multiple testing correction threshold is displayed by the dotted line and an asterisk. (b) A bar chart showing individual results from linear models with polygenic risk scores for BMI as the predictor. BMI-associated inflammatory markers are displayed on the x-axis, and negative log-transformed p-values for each inflammatory marker are displayed on the y-axis. Nominally significant associations are represented by a white bar.

631 **Figure 1**



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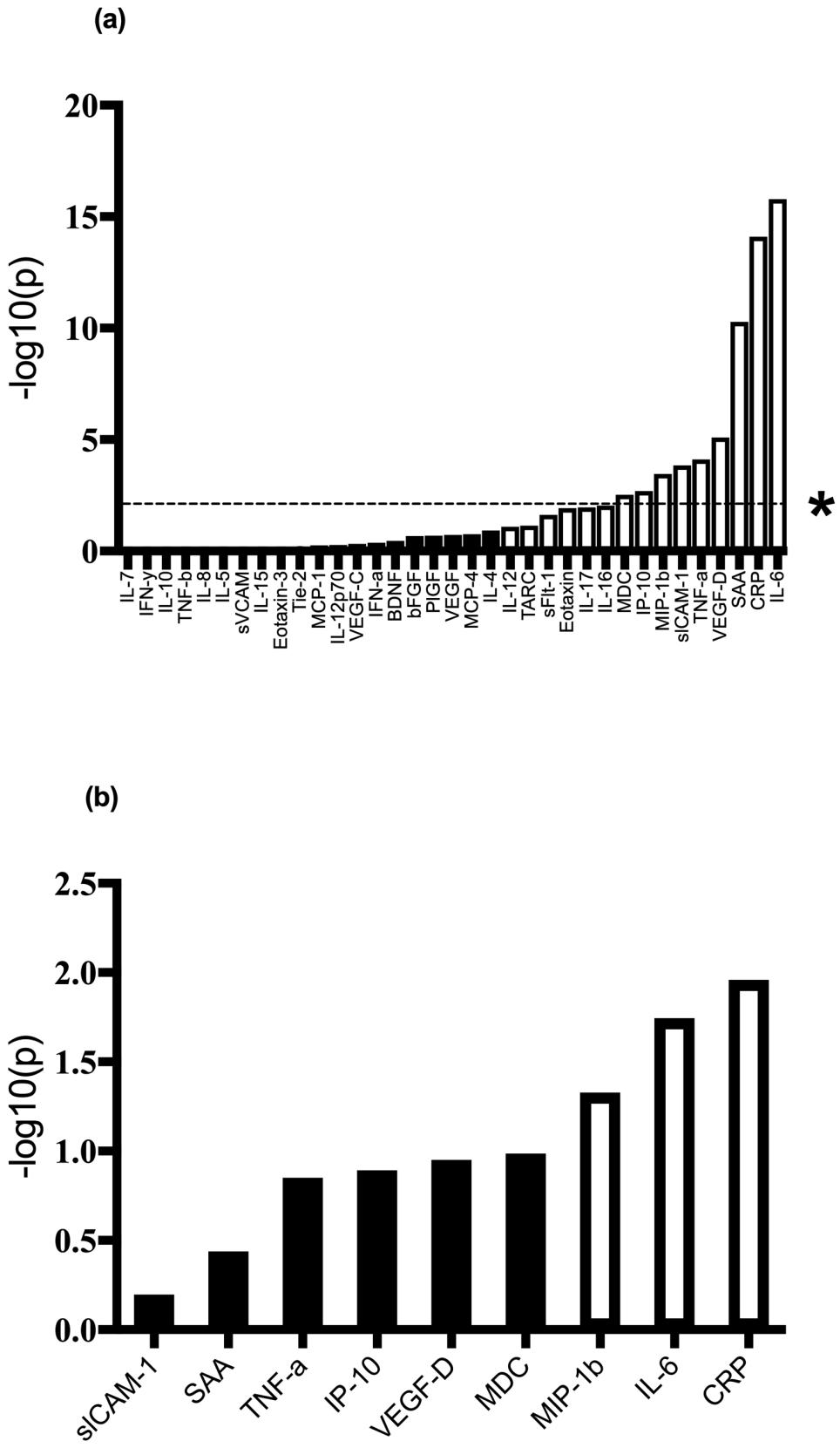
634 **Figure 2**



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