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# Cross-sectional association between metabolic parameters and psychotic-like experiences in a population-based sample of middle-aged and elderly individuals

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ABSTRACT

*Background:* Metabolic alterations are often found in patients with clinical psychosis early in the course of the disorder. Psychotic-like experiences are observed in the general population, but it is unclear whether these are associated with markers of metabolism.

*Methods:* A population-based cohort of 1890 individuals (mean age 58.0 years; 56.3% women) was included. Metabolic parameters were measured by body-mass index (BMI), concentrations of low-density and high-density lipoprotein cholesterol (LDL-C and HDL-C), total cholesterol, triglycerides, and fasting glucose and insulin in blood. Frequency and distress ratings of psychotic-like experiences from the positive symptom dimension of the Community Assessment of Psychic Experience questionnaire were assessed. Cross-sectional associations were analysed using linear regression analyses.

*Results:* Higher BMI was associated with higher frequency of psychotic-like experiences (adjusted mean difference: 0.04, 95% CI 0.02–0.06) and more distress (adjusted mean difference: 0.02, 95% CI 0.01–0.03). Lower LDL-C was associated with more psychotic-like experiences (adjusted mean difference: −0.23, 95% CI −0.40 to −0.06). When restricting the sample to those not using lipid-lowering medication, the results of BMI and LDL-C remained and an association between lower HDL-C and higher frequency of psychotic-like experiences was found (adjusted mean difference: −0.37, 95% CI −0.69 to −0.05). We observed no significant associations between cholesterol, triglycerides, glucose, insulin or homeostatic model assessment and psychotic-like experiences.

*Conclusions:* In a population-based sample of middle-aged and elderly individuals, higher BMI and lower LDL-C were associated with psychotic-like experiences. This suggests that metabolic markers are associated with psychotic-like experiences across the vulnerability spectrum.

## 1. Introduction

Traditionally, clinical psychosis has been conceptualized as a distinct disease entity, dividing the population into patients, who show symptoms of the disorder, and healthy individuals who do not. Epidemiological studies continue to challenge this clinical concept, as it has been convincingly shown that in the general population 7.2% report psychotic-like experiences. Importantly, for many individuals these psychotic-like experiences are not associated with clinical impairment (Kusztrits et al., 2020; Linscott and van Os, 2013). Of these individuals,

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20% develop persistent psychotic-like experiences and 7% clinical psychosis, with a prevalence below 1% internationally (Eaton et al., 1991; Kendler et al., 1996; van Os et al., 2000). Lastly, nearly all risk factors for clinical psychosis (e.g., demographic, personality, neurocognitive, environmental and genetic factors) predict greater risk of psychotic-like experiences in otherwise healthy individuals (van Os et al., 2009).

Over the years a large number of theories, mostly biological, on the etiology of the clinical schizophrenia syndrome have been brought forward (reviewed in Linscott & Van Os, 2010) (Linscott and van Os, 2010). This may raise the question whether the biological processes that are thought to underlie the clinical schizophrenia syndrome are also associated with psychotic-like experiences, arising in the normal population. However, this issue has been rarely addressed (Linscott and van Os, 2010). Several systemic biological factors have been shown to be associated with clinical psychosis, i.e., metabolic perturbations such as obesity, insulin resistance, dyslipidemia, type 2 diabetes, and inflammation (Hasnain et al., 2010). Commonly, associations between altered metabolic markers and psychosis are regarded as effects of antipsychotic use (Sabé et al., 2023). However, the association between metabolic perturbations and psychosis has evidently been observed before the use of antipsychotics (Kohen, 2004). More than 70 years ago, before the use of first-generation antipsychotics, many people diagnosed in these days with 'dementia praecox' showed abnormal responses to insulin and diabetes-like glucose tolerance curves. Recently, evidence has emerged showing that drug-naïve first-episode patients with clinical psychosis already portray changes in the glucose homeostasis, lipids and lipoproteins compared with healthy controls (Çakici et al., 2020; Guest et al., 2011; Pillinger et al., 2017; van Nimwegen et al., 2008). Hence, antipsychotic use or the long-term effects of psychotic disorders cannot entirely explain these associations. Interestingly, in a cohort study insulin resistance was present more often in schizophrenia patients and also, but with a slightly smaller ratio, in unaffected siblings compared with healthy controls (van Beveren et al., 2014). Therefore, with respect to psychotic-like experiences, a dysfunctional metabolism may also be found, albeit to a lesser extent, in presumed healthy individuals with psychotic-like experiences.

The current study addresses the question whether metabolic abnormalities are associated with the presence of psychotic-like experiences in the general population. We therefore investigated the association between parameters of metabolic status and psychotic-like experiences in participants from the Rotterdam study, a population-based cohort.

## 2. Methods

### 2.1. Terminology

Throughout the manuscript we comply to the terminology described by Feyaerts and colleagues relating to the description of clinical and subclinical psychotic phenomena (Feyaerts et al., 2021). Specifically, the term *clinical psychosis* is used when clinical features match specific criteria for psychotic disorders according to prevailing diagnostic tools, usually leading to clinical care and/or use of antipsychotics. The term *psychotic-like experiences* will be used to identify all psychotic experiences in the current general population-based study.

### 2.2. Study population and design

This cross-sectional investigation used data from the Rotterdam Study, a population-based cohort of 14,926 middle-aged and elderly individuals. Detailed information on the design of the Rotterdam Study has been published elsewhere (Ikram et al., 2017). Briefly, the design of the Rotterdam Study is that of a prospective cohort in the Ommoord district in Rotterdam, the Netherlands. Over the years several waves of participants were included; this study used data from a cohort that was initiated in 2006 in which 3932 individuals aged 45 and over were included. Between March 2007 and October 2008, questions on psychotic-like experiences were included, leading to a total of 1890 individuals with data on metabolic parameters and psychotic-like experiences.

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

### 2.3. Metabolic parameters

At the research facility, weight and height were measured on calibrated scales to calculate body mass index (BMI) ($kg/m^2$). Blood was taken to determine concentrations of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, glucose, and insulin which were measured in serum (mmol/L). HDL cholesterol was measured with the HDL-C cholesterol plus third-generation assay (Roche Diagnostics). Total cholesterol was measured by an automated enzymatic procedure by using the cholesterol oxidase phenol 4-aminoantipyrine peroxidase reagent agent (Roche Diagnostics, Indianapolis, IN). LDL-C cholesterol was calculated using the Friedewald formula (total cholesterol − HDL cholesterol − triglycerides/2.2). Concentrations of triglycerides were determined by an automated enzymatic procedure by using the glycerine phosphate oxidase peroxidase reagent agent (Roche Diagnostics). Glucose concentrations were measured using glucose hexokinase and insulin concentrations were measured by means of electrochemiluminescence immunoassay technology using a Roche Modular Analytics E170 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Only fasting glucose and insulin measurements were included in the analyses. Additionally, homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting serum glucose and fasting serum insulin levels divided by 22.5.

### 2.4. Assessment of psychotic-like experiences

To assess the presence of hallucinatory or delusional experiences (from the positive symptom dimension) participants completed 19 items of the Community Assessment of Psychic Experiences (CAPE; http://www.cape42.homestead.com) (Konings et al., 2006; Stefanis et al., 2002). The CAPE is a self-report questionnaire that assesses the frequency of psychotic-like experiences as well as the amount of distress caused by these psychotic-like experiences. Frequency and distress are both rated on a four-point scale, ranging from 'never' (0) to 'nearly always' (3) for experiencing psychotic symptoms, and from 'not distressed' (0) to 'very distressed' (3) with regard to distress. A maximum of 57 points could be obtained for both frequency and distress ratings. Individuals with frequent psychotic-like experiences were defined when they selected (2) 'often' or (3) 'nearly always' on at least one item of the frequency scale. Individuals with frequent distress of their psychotic-like experiences were selected in the same way using the distress scale. Research has shown that this questionnaire has good discriminative validity, family-specific variation and stability over time (Hanssen et al., 2003; Konings et al., 2006; Korver-Nieberg et al., 2011). As negative symptoms strongly overlap with symptoms of depression, only the positive symptom dimension of the CAPE was used in current analyses.

### 2.5. Other measurements

Ancestry was determined using genetic data to create ancestral populations based on having at least 50% genetic material from a respective ancestral group including European or non-European (e.g. East-Asian, African, Admixture). Education level was assessed during the home interview and categorized based on the international standard classification of education (primary/lower/intermediate/higher). Employment status was used as a binary variable (paid employment/no paid employment). Partnership status was also used as a binary variable (partner/no partner). Smoking was self-reported and categorized as current smoking, former smoker and never smoked a cigarette. Alcohol consumption was self-reported and converted to grams per day (one glass = 10 g). Diabetes mellitus was defined as a fasting blood glucose exceeding 126 mg/dL and/or use of blood glucose–lowering medication, hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg, and/or the use of blood pressure–lowering medication. Blood pressure was measured at the research facility. Anxiety disorder was assessed using the Munich version of the Composite International Diagnostic Interview. Depressive symptoms were assessed using the center for epidemiologic studies depression scale (CES-D), with a cut-off of CES-D $\geq$ 16 points to determine clinically relevant depressive symptoms. Lipid-lowering medication (statins, ezetimibe or fibrates), antidiabetic medication, and psychopharmacology use (antipsychotics, antidepressants, and hypnotics, sedatives or anxiolytics) were assessed by interview and cabinet check.

### 2.6. Statistical analyses

To assess the association between metabolic parameters and psychotic-like experiences, we conducted linear regression models with the respective metabolic marker as exposure parameter and the psychotic experience frequency and distress score as distinct outcomes. Residuals were distributed normally. Adjusted mean differences with corresponding 95% confidence intervals were estimated per point increase in the frequency psychotic-like experiences or perceived distress score. Analyses were run using 4 models: model 1 was adjusted for age and sex; model 2, the main model, expanded model 1 by additionally adjusting for ancestry, smoking, education level, employment status and having a partner; model 3 expanded model 2 by additionally adjusting for psychopharmacology use (i.e., antipsychotics, antidepressants, hypnotics or sedatives, and anxiolytics); model 4 expanded model 2 by additionally adjusting for anxiety disorder and depressive symptoms.

Next, we analysed the curvilinear association of BMI with psychotic-like experiences by adding a squared term of BMI to the model. We assume that the association between BMI and psychotic-like experiences may not be linear, since both a low and high BMI have been associated with psychiatric disorders (Andreassen et al., 2013; Meeuwsen et al., 2010; Sormunen et al., 2019). In addition, we also explored whether a curvilinear association may exist between the other metabolic parameters and psychotic-like experiences.

Finally, since lipid-lowering medication affects metabolic parameters, all analyses were rerun in participants who did not use any lipid-lowering medication ($n$ = 1446). To facilitate the interpretation of the findings, we also present the false discovery rates, using the Benjamini-Hochberg procedure (Benjamini, 1995), to account for multiple comparisons. Individuals with missing values for the frequency and/or distress ratings of psychotic-like experiences were excluded from the analyses. Analyses for the metabolic parameters were performed for the individuals for whom this data was available. As for the covariates, missing values of numeric data were imputed by the median value and missing values of categorical data were imputed by the most common class. Missing data on potential covariates did not exceed 1%. All analyses were performed in R software 3.4.0 (R Development Core Team, 2008).

## 3. Results

### 3.1. Study population characteristics

Table 1 shows the demographic and clinical characteristics of the study participants. In the study population 46.8% experienced at least one psychotic-like experiences and 10.2% experienced at least on time distress of their psychotic-like experiences (i.e., scoring at least one point on respectively the frequency and distress rating). “Scores for psychotic like experiences range from 0 to 26, and for associated distress from 0 to 22 (Fig. 1).”

**Table 1**
Demographic and clinical characteristics ($n$ = 1890).

| | |
|---|---|
| Age in years, mean (SD; range) | 58.0 (6.9; 46.5–89.4) |
| Sex, no. males (%) / no. females (%) | 826 (43.7) / 1064 (56.3) |
| Ancestry, no. (%) | |
| European | 1821 (96.4) |
| Other ethnicities | 69 (3.7) |
| Education level, no. (%) | |
| Primary education | 176 (9.3) |
| Lower/intermediate general education or lower vocational education | 648 (34.3) |
| Intermediate vocational education or higher general education | 521 (27.6) |
| Higher vocational education or university | 545 (28.8) |
| Paid employment, no. (%) | 1130 (59.8) |
| Having a partner, no. (%) | 1473 (77.9) |
| Smoking, no. (%) | |
| Current smoker | 452 (23.9) |
| Former smoker | 854 (45.2) |
| Never smoked | 584 (30.9) |
| Alcohol use in grams/day, median (IQR) | 6.4 (13.4) |
| Diabetes Mellitus, no. (%) | 180 (9.5) |
| Hypertension, no. (%) | 998 (52.8) |
| Anxiety disorder, no. (%) | 135 (7.1) |
| Clinically relevant depressive symptoms | |
| CES-D score, no. $\geq$ 16 (%) | 163 (8.6) |
| Medication use, no. (%) | |
| Antidiabetics | 95 (5.0) |
| Lipid reducing agents | 444 (23.5) |
| Anti-inflammatory and anti-rheumatic agents | 278 (14.7) |
| Antipsychotics | 9 (0.5) |
| Antidepressants | 103 (5.4) |
| Hypnotics or sedatives | 103 (5.4) |
| Anxiolytics | 93 (4.9) |
| Metabolic parameters | |
| BMI in kg/m$^2$, mean (SD) | 27.7 (4.6) |
| LDL (mmol/l), median (IQR) | 3.4 (1.3) |
| HDL (mmol/l), median (IQR) | 1.4 (0.6) |
| Total cholesterol (mmol/l), median (IQR) | 5.5 (1.4) |
| Triglycerides (mmol/l), median (IQR) | 1.3 (0.8) |
| Fasting glucose (mmol/l), median (IQR) | 5.3 (0.7) |
| Fasting insulin (mmol/l), median (IQR) | 79.0 (57.0) |
| At least *some psychotic experiences, frequency, no. (%) | 885 (46.8) |
| At least *some psychotic experiences, median (IQR) | 2.0 (3.0) |
| At least **some distress from psychotic experiences, no (%) | 192 (10.2) |
| At least **some distress from psychotic experiences, median (IQR) | 2.0 (2.0) |

Abbreviations: BMI, body mass index in units of kg/m$^2$; CAPE, Community Assessment of Psychic Experiences; CES-D, center for epidemiologic studies depression scale; HDL, high-density lipoproteins; IQR, interquartile range; LDL, low-density lipoproteins.
* A score of at least 1 on any item of the frequency scale from the Community Assessment of Psychic Experiences (CAPE) self-report questionnaire; ** A score of at least 1 on any item of the distress scale from the CAPE self report questionnaire.

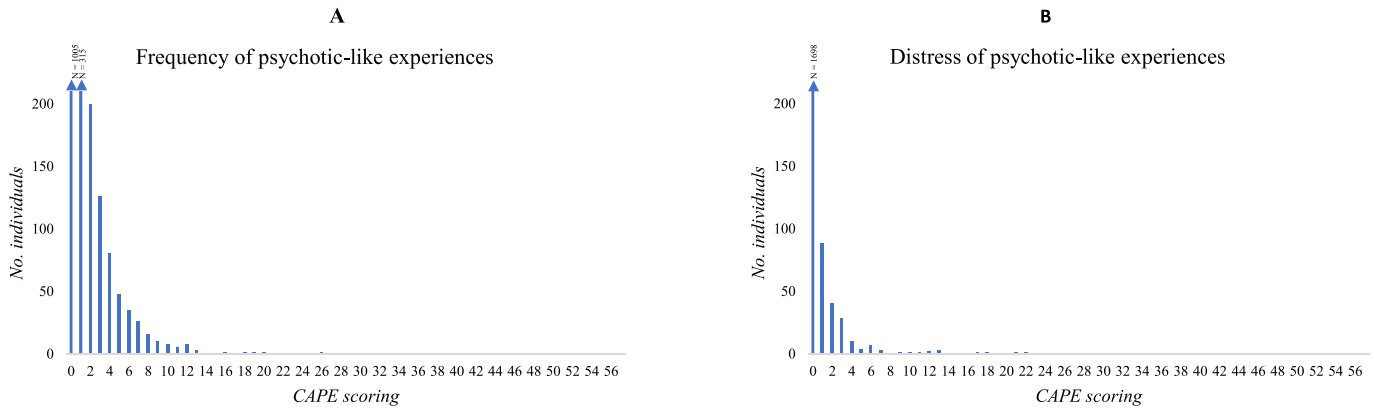


**Fig. 1.** Showing the distribution of (A) the frequency of psychotic-like experiences and (B) the distress of psychotic-like experiences from the Community Assessment of Psychic Experiences (CAPE) questionnaire. Frequency and distress are both rated on a four-point scale, ranging from 'never' (0) to 'nearly always' (3) for experiencing psychotic symptoms, and from 'not distressed' (0) to 'very distressed' (3) with regard to distress. A maximum of 57 points could be obtained for both frequency and distress ratings.

### 3.2. BMI

Higher BMI was associated with higher frequency of psychotic-like experiences (adjusted mean difference: 0.04, 95% CI 0.02 to 0.07) and with more distress (adjusted mean difference: 0.02; 95% CI: 0.01 to 0.04) when adjusting for age and sex (model 1; Supplementary Table 1). This association remained after adjustment for possible confounders, i.e. ancestry, smoking, education level, employment status and partnership status (frequency, adjusted mean difference: 0.04, 95% CI: 0.02 to 0.06, and distress, adjusted mean difference: 0.02, 95% CI: 0.01 to 0.03; model 2; Table 2). When we additionally adjusted for psychopharmacology use (model 3; Supplementary Table 2) and anxiety disorder or depressive symptoms (model 4; Supplementary Table 3) BMI remained associated with frequency and distress of psychotic-like experiences with similar effect sizes.

Next, we explored whether BMI was associated with frequency of psychotic-like experiences in a curvilinear model. In this model we observed that a higher BMI was significantly associated with a higher frequency of psychotic-like experiences, albeit with restricted effect sizes (Fig. 2, Supplementary Table 4). When exploring the curvilinear graph, it seems that individuals with lower BMI, i.e. underweight, or substantially higher BMI, i.e. obesity, seem to score higher on both the frequency and distress items, with the exemption of individuals that are normal-weight or overweight. For the other metabolic parameters no curvilinear association was observed.

### 3.3. Lipids

Lower LDL-C was associated with higher frequency of psychotic-like experiences after adjustment for age and sex (adjusted mean difference: −0.23, 95% CI: −0.41 to −0.06; Supplementary Table 1), which remained similar after confounder adjustment (adjusted mean difference: −0.23, 95% CI: −0.40 to −0.01; Table 2). These results remained when we additionally adjusted for psychopharmacology use and for anxiety disorder or depressive symptoms (supplementary Tables 2 and 3). No significant association was found between LDL-C and distress. Lower HDL-C was associated with higher frequency of psychotic-like experiences after adjustment for age and sex (adjusted mean difference: −0.33, 95% CI: −0.61 to −0.06), however, after further confounder adjustment no significant association was observed (adjusted mean difference: −0.26, 95% CI: −0.53 to 0.01). No significant associations were observed between HDL and distress. Total cholesterol was not significantly associated with either frequency or distress of psychotic-like experiences. Although an association was observed between triglycerides and a higher frequency of psychotic-like experiences after adjustment for only age and sex (adjusted mean difference: 0.15, 95% CI: 0.02 to 0.28), these associations did not remain after confounder adjustment (adjusted mean difference: 0.11, 95% CI: −0.03 to 0.23). No significant associations between triglycerides and psychotic-like experiences or distress were observed after adjustment for psychopharmacology use and for anxiety disorder or depressive symptoms.

### 3.4. Glucose homeostasis

Fasting glucose was associated with a higher frequency of psychotic-like experiences when adjusting for age and sex (adjusted mean difference: 0.11, 95% CI: 0.01 to 0.20; Supplementary Table 1), but these associations attenuated after confounder adjustment (adjusted mean difference: 0.08, 95% CI: −0.01 to 0.17; Table 2). After adjustment for psychopharmacology use and for anxiety disorder or depressive symptoms no significant associations were observed between fasting glucose and psychotic-like experiences or distress (supplementary Tables 2 and 3). Fasting glucose was not significantly associated with distress of psychotic-like experiences.

Higher insulin showed a restricted association with higher frequency of psychotic-like experiences after adjustment for age and sex and after confounder adjustment. Higher HOMA-IR was minimally associated with higher frequency of psychotic-like experiences when adjusting for age and sex. However, after further confounder adjustment no association was observed between HOMA-IR and psychotic-like experiences.

### 3.5. Sensitivity analysis

As a sensitivity analysis, we reran analyses only including participants who did not use any lipid-lowering medication ($n$ = 1446; Supplementary Table 5). The association between higher BMI and a higher frequency of psychotic-like experiences remained with a similar effects size (adjusted mean difference: 0.04, 95% CI: 0.01 to 0.07). However, the association between higher BMI and the level of distress was attenuated and did not remain (adjusted mean difference: 0.01, 95% CI: −0.01 to 0.03). Lower LDL-C was associated with higher frequency of psychotic-like experiences (adjusted mean difference: −0.26, 95% CI: −0.47 to −0.05) and also with a higher distress rate (adjusted mean difference: −0.13, 95% CI: −0.26 to −0.01). Additionally, we observed an association between lower HDL and a higher frequency of psychotic-like experiences (adjusted mean difference: −0.37, 95% CI: −0.69 to −0.05). In line with the analysis in the total study population, we did not observe any significant associations for the other metabolic parameters.

**Table 2**
Associations between metabolic markers and psychotic-like experiences, model 2: adjustment for possible confounders[a].

| Metabolic markers | Psychotic-like experiences | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Frequency | | | | Perceived distress | | | |
| | Adjusted mean difference | 95% CI | P | q | Adjusted mean difference | 95% CI | P | q |
| BMI (kg/m$^2$), $n = 1890$ | 0.04 | 0.017; 0.062 | < 0.001 | 0.006 | 0.019 | 0.005; 0.032 | 0.007 | 0.056 |
| Total cholesterol (mmol/l), $n = 1867$ | −0.043 | −0.143; 0.058 | 0.405 | 0.405 | −0.016 | −0.073; 0.040 | 0.57 | 0.76 |
| LDL-C (mmol/l), $n = 865$ | −0.225 | −0.395; −0.055 | 0.01 | 0.04 | −0.095 | −0.203; 0.013 | 0.084 | 0.336 |
| HDL-C (mmol/l), $n = 1867$ | −0.26 | −0.532; 0.012 | 0.061 | 0.098 | 0.001 | −0.152; 0.154 | 0.986 | 0.986 |
| Triglycerides (mmol/l), $n = 1867$ | 0.101 | −0.027; 0.230 | 0.122 | 0.139 | 0.055 | −0.017; 0.128 | 0.133 | 0.355 |
| Fasting glucose (mmol/l), $n = 1851$ | 0.078 | −0.014; 0.171 | 0.096 | 0.128 | 0.009 | −0.043; 0.061 | 0.732 | 0.837 |
| Fasting insulin (mmol/l), $n = 1799$ | 0.002 | 0.000; 0.003 | 0.042 | 0.098 | 0.0005 | −0.000; 0.001 | 0.264 | 0.432 |
| HOMA-IR, $n = 1795$ | 0.004 | 0.000; 0.008 | 0.050 | 0.098 | 0.001 | −0.001; 0.004 | 0.27 | 0.432 |

Abbreviations: BMI, body mass index in units of kg/m$^2$; CI, confidence interval; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein cholesterol; P, *p*-value; q, Benjamini-Hochberg procedure.
[a] Linear regression model adjusted for age, sex, ancestry, smoking, education level, employment status, and partnership status (model 2).

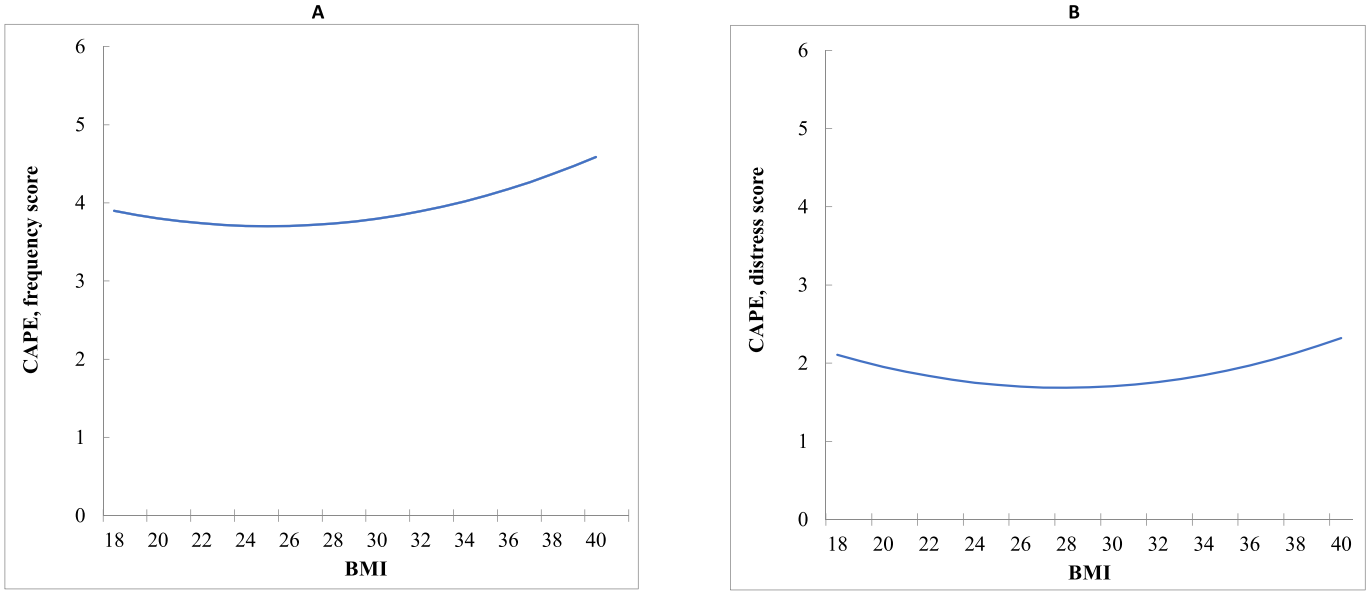


**Fig. 2.** The curvilinear association between body mass index (BMI) in kg/m$^2$ and the Community Assessment of Psychic Experience (CAPE) total score from A, CAPE total frequency score, and B, CAPE total distress score. Estimates of effect size were obtained from a linear regression model which was corrected for age, sex, ancestry, education level, employment status, and partnership status.

## 4. Discussion

In the current study we observed that higher BMI and lower LDL-C were associated with a higher frequency of psychotic-like experiences. In a sensitivity analysis of non-lipid-lowering medication users only, the results for BMI and LDL-C remained, and we additionally observed that lower HDL was associated with psychotic-like experiences. No significant association was found of total cholesterol, triglycerides, glucose, insulin and homeostatic model assessment with psychotic-like experiences.

The associations between metabolic parameters and psychotic-like experiences in the current study resemble, at least partially, the lipid alterations identified in first-episode drug-naïve or minimally treated clinical psychosis patients (Çakici et al., 2020; Pillinger et al., 2017). However, one should be cautious comparing the findings in the current study with the results obtained from patients with first-episode clinical psychosis. First-episode psychosis typically manifests at adolescence while our study included older individuals. Although some first-episode patients are older (Meesters et al., 2012), we are not aware of metabolic data on first-episode patients of older age. We suggest two possible explanations for the presence of similar associations of lipid metabolism expression in our sample. First, individuals with psychotic-like experiences may experience societal impediments due to the presence of prolonged psychotic-like experiences which in turn affect their general health and lifestyle, including unhealthy dietary habits. This may lead to increased BMI and lipid changes, such as lower HDL-C and higher LDL-C, although we observed lower LDL in the current study. Second, we cautiously hypothesize that the explanation for the associations we observed in individuals with psychotic-like experiences may be similar to the associations seen for first-episode clinical psychosis patients. In first-episode clinical psychosis patients decreased total- and LDL cholesterol levels and increased parameters of disturbed glucose metabolism are found. A recent study reported alterations of plasma metabolic profiles in medication-naïve patients with clinical high-risk for psychosis, a prodromal stage of clinical psychosis, which could discriminate them from healthy controls (Li et al., 2021). These alterations are thought to be intrinsic to the disorder, i.e., molecular pathways underlying both clinical psychosis and metabolic dysregulation (Liu et al., 2013). One such factor may be an altered immune status as there is robust evidence of immune dysregulation in antipsychotic-naïve first-episode clinical psychosis patients, including elevated peripheral levels of adipocytokines interleukin 6 and tumor necrosis factor alpha (Çakici et al., 2020). Indeed, metabolic and inflammatory compounds regulate and in some cases dysregulate each other (Bernardi et al.,

2018). Therefore, similar immune alterations may be present in individuals with psychotic-like experiences. However, no extensive data on inflammation was available for the current subset in this study. Thus, although the association between a high BMI and psychotic-like experiences in our study population could be the effect of poor lifestyle habits, the evidence outlined above may alternatively suggest a bidirectional relationship between changes in markers of metabolism, and psychotic-like experiences. Interestingly, a genome wide association study identified overlapping genetic mechanisms for clinical psychosis and BMI and blood lipids (including LDL-C, HDL, and triglycerides), which also might suggest a shared cause of altered metabolic health and clinical psychosis (Andreassen et al., 2013).

Taken together, our population-sample consists of relatively older individuals compared to first-episode psychosis patients, but some are experiencing psychotic-like experiences potentially for a prolonged time, that do not result in a clinical diagnosis. Because of this, in addition to the genetic vulnerability described above, they may be more prone to a unhealthy lifestyle resulting in a higher BMI for example. However, our results of lower LDL-C are comparable to those found in first-episode patients with schizophrenia. Therefore, we cautiously suggest that our sample of individuals with psychotic-like experiences may be more similar to first-episode patients as compared to either subjects from the normal population and patients with a long-standing diagnosis of psychosis (Binbay et al., 2012).

In the current population study 46.8% reported at least one psychotic-like experience and 28.5% reported to have frequent psychotic-like experience. The percentage of experiencing distress of these psychotic-like experiences was more than four times lower. In a recent study on 3234 adolescents during COVID-19 lockdown, using the CAPE-P15, more individuals experienced at least one psychotic-like experiences (51.4%), but the percentage of individuals experiencing frequent psychotic-like experiences was lower (11.6%) as compared to our population (Wang et al., 2023). It is difficult to determine why these prevalence numbers of psychotic-like experiences are higher than earlier epidemiological studies have published, i.e. 7.2% (Linscott and van Os, 2013). The CAPE self-report questionnaire may be more sensitive to psychotic-like experiences than other measurement tools or more individuals are experiencing psychotic-like experiences than previously thought. We are not aware of another large-scale study on psychotic-like experiences in middle-aged and elderly individuals using the CAPE self-report questionnaire. We cautiously suggest that psychotic-like experiences, without transitioning to a psychiatric disorder, may persist in some individuals for a prolonged time, and therefore these experiences are more often found in older age. The distress rating of psychotic-like experiences was not provided by these aforementioned population studies.

The majority of individuals in our study that report psychotic-like experiences do not report distress. This may be an important factor contributing to the absence of clinical severity in this group. From psychological research it is well known that individuals that subjectively feel 'in control' of psychotic-like experiences are less disturbed and distressed by them or even feel that the psychotic-like experiences they experience are supportive (Daalman et al., 2011). A longitudinal general population study suggested that emotional appraisal and degree of intrusiveness of psychotic-like experiences are modifiers for clinical outcome (Hanssen et al., 2005). Therefore, the development of distress and subsequently clinical severity may depend on additional psychosocial factors (Kahn et al., 2015).

This is one of the first studies to assess psychotic-like experiences in a population-based sample at a large scale, this ensures generalizability to a larger population. A limitation of our study is that we could only analyse the data cross-sectionally, and therefore are not able to investigate or infer any temporal relationship between psychotic-like experiences and BMI or other metabolic parameters. Furthermore, only the positive symptom dimension from the CAPE questionnaire was used so we do not have data on the presence or absence of negative psychotic-like experiences. In addition, some individuals in this study may have met or have met the criteria for clinical psychosis. However, the prevalence of psychotic disorders in the general population is low (Fischer and R.W., 2020), additionally only a fraction in our study population received psychopharmacological treatment, suggesting that the effect of unknown clinical psychosis on our results is probably small. Lastly, the concept of psychotic-like experiences is not narrowly defined and differs among respective literature.

In the current study of a large community sample, we found that higher BMI and lower LDL-C are associated with higher frequency of psychotic-like experiences, resembling associations found in clinical psychosis. Further research should focus on investigating cause-effect relationships between psychotic-like experiences and metabolic markers, identifying factors that determine the trajectory towards the phenotypical expression of psychotic disorder, and improving preventive and treatment strategies regarding metabolic dysfunctions prevalent in people with clinical and nonclinical psychotic-like experiences.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.09.008.

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## Credit authorship contribution statement

A.I. Luik, N.J.M. van Beveren, N. Çakici, N.H Grootendorst-van Mil, S. J. Roza and H. Tiemeier designed the research. N. Çakici and N.H Grootendorst-van Mil analysed and visualised the data. N.J.M. van Beveren, A.I. Luik, N. Çakici, N.H Grootendorst-van Mil and L. de Haan drafted the article and S.J. Roza, T. Voortman and H. Tiemeier made critical revisions related to important intellectual content of the manuscript.

## Declaration of competing interest

None.

## Data availability

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

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