APOE E4 is associated with hyperlipidemia and obesity in elderly schizophrenic patients

Wei Li1,2, Fengju Liu3,4, Rui Liu3,4, Xinmei Zhou4, Guanjun Li4* & Shifu Xiao1,2*

Obesity is a critical issue in patients with schizophrenia, which is considered to be brought about by both environmental and genetic factors. Apolipoprotein E (APOE) gene polymorphisms might be involved in the pathogenesis of schizophrenia, however, the effect of APOE gene polymorphism on obesity has never been investigated in Chinese aging with schizophrenia. This cross-sectional study was to investigate the effect of obesity on cognitive and psychiatric symptoms in elderly participants with schizophrenia. At the same time, we also discussed the inner link between APOE E4 and obesity. 301 elderly participants with schizophrenia and 156 normal controls were included in the study. Their cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), psychiatric symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), and APOE gene polymorphism was determined by polymerase chain reaction (PCR). The prevalence of obesity in elderly schizophrenic patients and healthy controls accounted for 15.9% (48/301) and 10.3% (16/156), respectively, with no statistically significant difference. By using stepwise linear regression analysis, we found that elevated fasting blood glucose, hypertension, and hyperlipidemia were risk factors for obesity in elderly schizophrenic patients. Although there was no direct correlation between APOE E4 and obesity in patients with schizophrenia, it was significantly correlated with hyperlipemia ($r = -0.154$, $p = 0.008$), suggesting that APOE E4 may induce obesity in elderly patients with schizophrenia through hyperlipemia. However, the above conclusions do not apply to the normal elderly. What’s more, we did not find a link between obesity and cognitive function or mental symptoms for both patients with schizophrenia and normal controls. APOE E4 is associated with hyperlipidemia in elderly schizophrenic patients, which may be a risk factor for obesity, however, the above conclusion does not apply to the normal elderly.

**Abbreviations**

APOE  Apolipoprotein E  
MoCA  The Montreal Cognitive Assessment  
GDS  The Geriatric Depression Scale  
PANSS  The Positive and Negative Syndrome Scale  
PCR  Polymerase chain reaction  
MetS  Metabolic syndrome  
BMI  Body mass index  
HDL  High density lipoprotein  
FDG  Fasting plasma glucose  
LDL  Low-density lipoprotein  
MCI  Mild cognitive impairment  
AD  Alzheimer's disease

Obesity is a critical issue in patients with schizophrenia, which can adversely affect the risk of cardiovascular disorders, adult-onset diabetes mellitus, quality of life, non-adherence with pharmacological interventions as
well as psychiatric readmissions. According to previous studies, obesity will affect 40–60% of people with schizophrenia. Although some studies have shown that second-generation antipsychotics are the main cause of obesity, others have shown that unhealthy lifestyle, socioeconomic disadvantages, and premonitory genetic vulnerabilities may also play an important role.

Apolipoprotein E (APOE) E4 allele is the largest genetic risk factor for Alzheimer's disease (AD), and it has been confirmed to be associated with the accelerated development of cognitive deficits and increased in myelin breakdown. Due to a similar decline in specific cognitive domains, Harrington et al. first hypothesized that APOE might also play an important role in schizophrenia. However, the association between schizophrenia and APOE is complex, and the relevant conclusions are inconsistent, for example, a meta-analysis of 17 studies has shown that APOE E4 is a risk factor for schizophrenia, while another meta-analysis of 28 association studies did not present the above conclusions.

In the last decades, the APOE gene has been confirmed to be associated with obesity, and many studies have shown that APOE is associated with obesity symptoms in AD patients. However, only two studies have examined the association between APOE and obesity in schizophrenia patients, one of which shows that the APOE expression in the hippocampus in schizophrenic patients is significantly higher than that in the control group, while the other showed that APOE gene could influence the prevalence of diabetes and possibly overweight in psychiatric patients, and the mechanism may involve lipid metabolisms.

So far, there is no study on the relationship between obesity and apoE gene polymorphism in Chinese elderly schizophrenic patients, therefore, we conducted this cross-sectional study to investigate the relationship between APOE E4 and lipid metabolism and obesity.

Materials and methods

Participants. This cross-sectional study included 301 elderly patients with schizophrenia and 156 normal controls. Details can be found in our previous study. The inclusion criteria were as follows: (1) aged 60 or more; (2) without major medical abnormalities, including unstable, acute, or life-threatening medical illness, and central nervous system diseases; (3) was able to cooperate and complete relevant inspections. Through face-to-face interviews and medical records, we obtained general demographic data (such as age, education, gender, BMI, duration of disease), daily living habits (smoking, drinking, drinking tea, physical exercise, hobby), disease history (hypertension, diabetes, and hyperlipidemia) and currently prescribed medicines (clozapine, olanzapine, quetiapine, risperidone, aripiprazole) of the subjects.

This study was subject to approval by the Research Ethical Committee of the affiliated mental health center of Shanghai Jiaotong University School of Medicine. And written informed consent was obtained from all participants before the study. All research processes were conducted under the principles of the Declaration of Helsinki.

Clinical psychiatric assessment. Schizophrenia was diagnosed by two senior psychiatrists according to the International Classification of Diseases 10 diagnostic standards, while normal controls needed to exclude dementia and mild cognitive impairment (MCI).

Cognitive assessment and psychotic symptoms assessment. The Montreal Cognitive Assessment (MoCA) was used to evaluate the cognitive function of all the participants, while the Positive and Negative Syndrome Scale (PANSS) was utilized to assess the symptoms and severity of schizophrenia. What's more, we also used the Geriatric Depression Scale (GDS) to exclude depression.

Genotyping of APOE and biochemical detection of blood lipids. All the subjects stopped eating after 9 p.m. and their peripheral blood was collected between 7:00 a.m. and 9:00 a.m (the next morning). Anticoagulant tubes and clot activating gel-containing serum separator tubes were used to assay blood indexes, such as cholesterol, triglyceride, fasting plasma glucose (FGD), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Genomic DNA was extracted from blood cells (after high-speed centrifugation) by using a Blood Genomic DNA Extraction Kit (Qiagen NV, Venlo, the Netherlands), and multiplex amplification refractory mutation system polymerase chain reaction (PCR) was used to determine the APOE genotype. According to the method described earlier, APOE E4 included ε2/ε4, ε3/ε4, and ε4/ε4, while Non-APOE E4 types included ε2/ε2, ε2/ε3 and ε3/ε3.

Statistical analysis. Continuous variables were expressed as mean ± SD and categorical variables were expressed as frequencies (%). The single sample Kolmogorov–Smirnov test was used to test whether the data conform to the normal distribution. Independent sample t-test was used to compare the data of normal distribution between the obesity group and the non-obesity group, Mann–Whitney U test was used to compare the data of non-normal distribution, while the Chi-square test was used to categorical variables between the two groups. Stepwise linear regression analysis for screening risk factors of obesity and partial correlation analysis was utilized to explore the association between APOE E4 and blood lipids (gender was controlled). All statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA), and two-tailed tests were utilized at a significance level of p < 0.05.

Ethics approval and consent to participate. All the subjects signed an informed consent form at the start of the study, and ethical approval was obtained from the Shanghai Mental Health Center.

Consent for publication. Not applicable.
Results

Table 1 displays the characteristic of subjects with different weight statuses (BMI ≥ 28 was considered as obesity). The prevalence of obesity in elderly patients with schizophrenia was 15.9% (48/301), and obesity patients were more likely to be female, with higher BMI, fasting blood glucose, and a higher proportion of diabetes, hypertension, and hyperlipidemia (p < 0.05), while there were no significant difference (p > 0.05) in age, education, duration of disease, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, APOE E4, smoker, drinker, tea drinker, physical exercise, hobby, clozapine, olanzapine, quetiapine, risperidone, aripiprazole and scores of MoCA, GDS, and PANSS between the obesity group and the non-obesity group. The results of stepwise regression analysis showed that fasting blood glucose (t = 4.025, p < 0.001*, 95% CI 0.333–0.970), hyperlipidemia (t = 3.445, p = 0.001, 95% CI 0.686–2.515) and hypertension (t = 2.499, p = 0.013, 95% CI 0.249–2.097) were risk factors for obesity. Table 2 presents the results. Then by using the partial correlation analysis and controlling gender, we found that APOE E4 was associated was hyperlipidemia (r = −0.154, p = 0.008), but not with hypertension or diabetes (p > 0.05).

Table 1. General demographic data of the Chinese elderly with schizophrenia based on obesity. BMI body mass index, MoCA Montreal Cognitive Assessment, GDS Geriatric Depression Scale, PANSS Positive and Negative Syndrome Scale. *Means p < 0.05.

| Variables                              | Obesity (N=48) | Non-obesity (N=253) | t or X2 | p |
|----------------------------------------|----------------|---------------------|---------|---|
| Age, y                                  | 67.54 ± 7.520  | 67.25 ± 6.487       | 0.275   | 0.783 |
| Education, y                           | 7.25 ± 3.540   | 8.17 ± 3.725        | −1.577  | 0.116 |
| Duration of disease, y                 | 35.04 ± 12.976 | 36.39 ± 13.265      | −0.645  | 0.519 |
| BMI, kg/m²                              | 30.17 ± 2.500  | 22.62 ± 3.178       | 15.575  | <0.001* |
| Fasting blood glucose, mmol/L,         | 6.20 ± 0.031   | 5.36 ± 1.233        | 3.846   | <0.001* |
| Triglyceride, mmol/L                   | 1.48 ± 0.571   | 1.37 ± 0.866        | 0.905   | 0.366 |
| Total cholesterol, mmol/L              | 4.68 ± 0.215   | 4.73 ± 0.987        | −0.298  | 0.766 |
| High density lipoprotein, mmol/L       | 1.23 ± 0.401   | 1.31 ± 0.408        | −1.207  | 0.228 |
| Low density lipoprotein, mmol/L        | 2.86 ± 0.989   | 2.74 ± 0.750        | 0.934   | 0.351 |
| Male, n (%)                            | 19 (39.6)      | 142 (56.1)          | 4.438   | 0.041* |
| APOE E4, n (%)                         | 9 (18.8)       | 47 (18.6)           | 0.001   | 1.000 |
| Hypertension, n (%)                    | 26 (54.2)      | 85 (33.6)           | 7.334   | 0.009* |
| Diabetes, n (%)                        | 24 (50.0)      | 54 (21.3)           | 17.257  | <0.001* |
| Hyperlipidemia, n (%)                  | 26 (54.2)      | 94 (37.2)           | 4.871   | 0.036* |
| Smoker, n (%)                          | 14 (29.2)      | 83 (32.8)           | 0.245   | 0.737 |
| Drinker, n (%)                         | 5 (10.4)       | 28 (11.1)           | 0.017   | 1.000 |
| Tea drinker, n (%)                     | 10 (21.3)      | 56 (22.1)           | 0.017   | 1.000 |
| Physical exercise, n (%)              | 16 (33.3)      | 79 (31.2)           | 0.083   | 0.866 |
| Hobby, n (%)                           | 15 (31.2)      | 94 (37.2)           | 0.609   | 0.513 |
| Clozapine, n (%)                       | 4 (8.3)        | 44 (17.4)           | 2.470   | 0.135 |
| Olanzapine, n (%)                      | 14 (29.2)      | 68 (26.9)           | 0.107   | 0.727 |
| Quetiapine, n (%)                      | 7 (14.6)       | 35 (13.8)           | 0.019   | 0.824 |
| Risperidone, n (%)                     | 13 (27.1)      | 74 (29.2)           | 0.092   | 0.863 |
| Aripiprazole, n (%)                    | 9 (18.8)       | 46 (18.2)           | 0.009   | 1.000 |
| MoCA                                   | 13.60 ± 6.180  | 13.89 ± 7.047       | −0.249  | 0.803 |
| GDS                                    | 10.23 ± 6.245  | 10.17 ± 5.820       | 0.055   | 0.957 |
| PANSS total score                      | 63.84 ± 19.737 | 64.64 ± 22.038      | −0.222  | 0.825 |
| Positive score                         | 11.60 ± 6.310  | 12.20 ± 5.997       | −0.586  | 0.558 |
| Negative score                         | 17.81 ± 7.664  | 18.92 ± 8.730       | −0.765  | 0.445 |
| General score                          | 33.42 ± 9.818  | 33.13 ± 11.039      | 0.158   | 0.874 |

Table 2. The results of Stepwise linear regression analysis (take obesity as the dependent variable). *Means p < 0.05.

| Variables            | B     | S.E  | t     | p      | 95% confidence interval |
|----------------------|-------|------|-------|--------|-------------------------|
| Fasting blood glucose| 0.652 | 0.162| 4.025 | <0.001*| 0.333–0.970             |
| Hyperlipidemia       | 1.600 | 0.465| 3.445 | 0.003* | 0.686–2.515             |
| Hypertension         | 1.173 | 0.469| 2.499 | 0.013  | 0.249–2.097             |
In order to verify whether the above conclusions still hold in the normal elderly, we recruited a group of normal controls, and their general demographic data are listed in Table 3. The prevalence of obesity in the normal elderly was 10.3% (16/156), and there was no significant difference (p > 0.05) in age, education, fasting blood glucose, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, APOE E4, gender, smoker, drinker, tea drinker, physical exercise, hobby, scores of MoCA and GDS between the obesity group and the non-obesity group, what’s more, APOE E4 was not associated with fasting blood glucose, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, diabetes, hypertension and hyperlipidemia (p > 0.05).

### Discussion

To my knowledge, this was the first study to explore the association between APOE E4 and obesity in elderly schizophrenic patients, and we found that (1) The prevalence of obesity in elderly patients with schizophrenia was 15.9%, and its risk factors included elevated fasting blood glucose, hypertension, and hyperlipidemia; (2) APOE E4 was associated with hyperlipidemia, but not with hypertension or diabetes in elderly schizophrenic patients; (3) APOE E4 was not associated with hyperlipidemia, hypertension or diabetes in the normal elderly.

In our study, we found that the prevalence of obesity in elderly patients with schizophrenia was 15.9%, but there was no difference in the prevalence of obesity between elderly schizophrenics and normal controls. In Yang Tian et al.’s study, they found that the prevalence of obesity in Chinese patients with chronic schizophrenia was 16.4%25. In Juan Wang et al.’s study, they found that the prevalence of obesity in patients with schizophrenia was 16.3%, which was not different from that (11.0%) of normal controls26. So our conclusions were consistent. However, in Aniyizhai Annamalai et al.’s study27, they found that the prevalence of obesity in patients with schizophrenia was 58.5%, which was significantly higher than that (27%) in the population control, and in Mythily Subramaniam et al.’s study, they found that the prevalence of obesity (73.6%) in patients with schizophrenia was significantly higher than that in controls28. We speculated that the above differences were mainly due to ethnic differences and different definitions of obesity.

Metabolic syndrome (MetS) is defined by the presence of three or more of the following five criteria: hypertension, hypertriglyceridemia, low HDL cholesterol level, increased waist circumference, and high fasting glucose concentration29. A high prevalence of MetS has been reported repeatedly in patients with schizophrenia30–32, and it has obvious interaction with obesity33. According to the definition of the International Diabetes Federation, abdominal obesity is central to the MetS34, while other studies showed that obesity is also a risk factor for metabolic syndrome35,36. In the current study, we found that elevated fasting blood glucose, hypertension, and hyperlipidemia were risk factors for obesity in elderly schizophrenics. So our conclusions were consistent, and schizophrenia patients prone to metabolic syndrome and obesity were mainly due to the administration of second-generation antipsychotics37,38 and bad living habits, such as smoking, drinking, and lack of exercise39.

Next, we explored the association between APOE E4 and obesity in elderly schizophrenic patients. Although we did not find an increased expression of APOE E4 in obese schizophrenic patients, we found that APOE E4 was closely related to hyperlipidemia. However, the above conclusion was not applicable in the normal control

| Variables                  | Obesity (N = 16) | Non-obesity (N = 140) | t or X² | p     |
|----------------------------|------------------|-----------------------|---------|-------|
| Age, y                     | 70.63 ± 7.982    | 69.75 ± 7.589         | 0.435   | 0.664 |
| Education, y               | 8.75 ± 4.669     | 9.89 ± 3.929          | −1.074  | 0.285 |
| Fasting blood glucose, mmol/L | 5.51 ± 1.099   | 5.54 ± 1.493          | 0.180   | 0.857 |
| Triglyceride, mmol/L       | 2.88 ± 2.968     | 1.82 ± 1.136          | 1.418   | 0.176 |
| Total cholesterol, mmol/L  | 5.36 ± 0.979     | 4.89 ± 1.080          | 1.652   | 0.101 |
| High density lipoprotein, mmol/L | 1.17 ± 0.332   | 1.19 ± 0.264          | −0.263  | 0.793 |
| Low density lipoprotein, mmol/L | 3.05 ± 0.902   | 2.92 ± 0.834          | 0.611   | 0.542 |
| BMI, kg/m²                 | 30.85 ± 2.455    | 25.38 ± 2.496         | 11.356  | <0.001* |
| Male, n (%)                | 4 (25.0)         | 57 (40.7)             | 1.489   | 0.285 |
| APOE E4, n (%)             | 4 (25.0)         | 21 (15.0)             | 1.067   | 0.291 |
| Hypertension, n (%)        | 8 (50.0)         | 71 (50.7)             | 0.003   | 1.000 |
| Diabetes, n (%)            | 1 (6.2)          | 14 (10.0)             | 0.232   | 1.000 |
| Hyperlipidemia, n (%)      | 3 (18.8)         | 23 (16.4)             | 0.056   | 0.732 |
| Smoker, n (%)              | 2 (12.5)         | 33 (23.6)             | 1.011   | 0.527 |
| Drinker, n (%)             | 2 (12.5)         | 28 (20.0)             | 0.520   | 0.739 |
| Tea drinker, n (%)         | 9 (56.2)         | 59 (42.1)             | 1.162   | 0.300 |
| Physical exercise, n (%)   | 10 (62.5)        | 91 (65.0)             | 0.039   | 1.000 |
| Hobby, n (%)               | 7 (43.8)         | 87 (62.1)             | 2.208   | 0.182 |
| MoCA                      | 24.13 ± 3.481    | 25.22 ± 3.759         | −1.113  | 0.267 |
| GDS                       | 5.69 ± 3.361     | 5.38 ± 4.444          | 0.269   | 0.788 |

Table 3. General demographic data of the Chinese elderly with normal cognitive function based on obesity. BMI body mass index, MoCA Montreal Cognitive Assessment, GDS Geriatric Depression Scale. *Means p < 0.05.
group. Utterman et al. found that isoform E4 was significantly more frequent in patients with hypercholesterolemia than normal controls40. Maria Odete Rodrigues et al.41 found that the epsilon4 allele was more frequent in dyslipidemic than normolipidemic subjects. What’s more, Zhang et al. found that the genotype of apoE4 was associated with higher serum total cholesterol, and APOE levels when compared with the genotypes E3 and E242. So our conclusions were consistent.

Finally, we also discussed the relationship between obesity and neuropsychological tests and psychiatric symptoms in schizophrenic patients, but we did not find that obese patients showed poorer cognitive function or more psychotic symptoms, and the same conclusion was also found in normal elderly people. Nur Amirah Abdul Rashid et al.45 found that there was no significant direct effect of BMI on cognition, when cognition was regressed on age, BMI, years of education, and diagnosis of schizophrenia. Depp et al.46 found that obesity was associated with worse global cognitive ability in bipolar disorder, but not in schizophrenia. Janney et al. also pointed out that there was no association between obesity and PANSS psychiatric symptoms45. However, other studies have shown the opposite conclusion that obesity was a risk factor for cognitive impairment or rich psychiatric symptoms in schizophrenia46–50. Therefore, the relationship between obesity and cognitive and mental symptoms needs to be further studied.

Sirtuin1 (SIRT1) belongs to a highly conserved family of protein deacetylase, which is involved in a variety of biological processes, such as cell proliferation, energy metabolism, as well as survival, chromatin dynamics and DNA repair51. Previous studies have shown that the SIRT1 gene may play an important role in the pathophysiology of schizophrenia, bipolar disorder, and Alzheimer’s disease, but the exact mechanisms are unclear52–54. In recent years, researchers have also proved that SIRT1 gene regulates obesity and lipid metabolism, for example, Thaddeus et al.55 pointed out that SIRT1 gene may affect obesity by regulating fatty acid oxidation in the liver, influencing obesity-induced inflammation in the liver and as well as modulating the activity of the circadian clock in metabolic tissues. In addition, the interaction between APOE and SIRT1 may also have an impact on individual’s obesity and cognition56, for instance, Jesus Campagna et al.57 found that the expression of APOE E4 would decrease the level of SIRT1 in serum and brain tissue of AD patients as compared to normal controls; Veena et al.58 found that APOE E4 could reduce the expression of SIRT1 and thus played a neuroprotective role; what’s more, María Teresa Flores-Dorantes et al.59 also found that SIRT1 gene could be affected by APOE gene, and then regulated obesity. Therefore, we hypothesized that obesity in patients with schizophrenia may also be influenced by APOE E4 and SIRT1 genes, but these conclusions need to be verified in future studies.

There are two limitations to our study. First, this is a cross-sectional study, unable to establish the causal relationship between APOE E4, cognitive function, and mental symptoms. Second, a relatively small sample size reduces the reliability of the study.

Conclusions
APOE E4 is associated with hyperlipidemia in schizophrenic patients, which may be a risk factor for obesity in schizophrenic patients, however, the above conclusion does not apply to the normal elderly.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 20 November 2020; Accepted: 30 June 2021
Published online: 20 July 2021

References
1. Mann, P. et al. Weight gain and obesity in schizophrenia: Epidemiology, pathobiology, and management. Acta Psychiatr. Scand. 132(2), 97–108 (2015).
2. An, H. et al. Obesity, altered oxidative stress, and clinical correlates in chronic schizophrenia patients. Transl. Psychiatry. 8(1), 258 (2018).
3. Weiden, P. J., Mackell, J. A. & McDonnell, D. D. Obesity as a risk factor for antipsychotic noncompliance. Schizophr. Res. 66(1), 51–57 (2004).
4. Huang, X. F., Weston-Green, K. & Yu, Y. Decreased SIRT1 expression and thus played a neuroprotective role; what’s more, María Teresa Flores-Dorantes et al.59 also found that SIRT1 gene could be affected by APOE gene, and then regulated obesity. Therefore, we hypothesized that obesity in patients with schizophrenia may also be influenced by APOE E4 and SIRT1 genes, but these conclusions need to be verified in future studies.

There are two limitations to our study. First, this is a cross-sectional study, unable to establish the causal relationship between APOE E4, cognitive function, and mental symptoms. Second, a relatively small sample size reduces the reliability of the study.

Conclusions
APOE E4 is associated with hyperlipidemia in schizophrenic patients, which may be a risk factor for obesity in schizophrenic patients, however, the above conclusion does not apply to the normal elderly.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 20 November 2020; Accepted: 30 June 2021
Published online: 20 July 2021

References
1. Mann, P. et al. Weight gain and obesity in schizophrenia: Epidemiology, pathobiology, and management. Acta Psychiatr. Scand. 132(2), 97–108 (2015).
2. An, H. et al. Obesity, altered oxidative stress, and clinical correlates in chronic schizophrenia patients. Transl. Psychiatry. 8(1), 258 (2018).
3. Weiden, P. J., Mackell, J. A. & McDonnell, D. D. Obesity as a risk factor for antipsychotic noncompliance. Schizophr. Res. 66(1), 51–57 (2004).
4. Huang, X. F., Weston-Green, K. & Yu, Y. Decreased SIRT1 expression and thus played a neuroprotective role; what’s more, María Teresa Flores-Dorantes et al.59 also found that SIRT1 gene could be affected by APOE gene, and then regulated obesity. Therefore, we hypothesized that obesity in patients with schizophrenia may also be influenced by APOE E4 and SIRT1 genes, but these conclusions need to be verified in future studies.

There are two limitations to our study. First, this is a cross-sectional study, unable to establish the causal relationship between APOE E4, cognitive function, and mental symptoms. Second, a relatively small sample size reduces the reliability of the study.
14. Moser, V. A. & Pike, C. J. Obesity and sex interact in the regulation of Alzheimer’s disease. *Neurosci. Biobehav. Rev.* 67, 102–118 (2016).
15. Keller, L. et al. The obesity related gene, FTO, interacts with APOE, and is associated with Alzheimer’s disease risk: A prospective cohort study. *J. Alzheimers Dis.* 23(3), 461–469 (2011).
16. Brietzke, E. et al. The impact of body mass index in gene expression of reelin pathway mediators in individuals with schizophrenia and mood disorders: A post mortem study. *J. Psychiatr. Res.* 102, 186–191 (2018).
17. Clark, D. et al. Apolipoprotein-E gene variants associated with cardiovascular risk factors in antipsychotic recipients. *Eur. Psychiatry.* 24(7), 456–463 (2009).
18. Li, W. et al. Associations between the apolipoprotein E e4 allele and reduced serum levels of high density lipoprotein a cognitively normal aging Han Chinese population. *Front. Endocrinol. (Lausanne).* 10, 827 (2019).
19. Qi, Q. et al. Cognitive decline is related to high blood glucose levels in older Chinese adults with the ApoE ε3/ε3 genotype. *Transl. Neurodegener.* 8, 12 (2019).
20. Ban, C. X. et al. Enhanced diabetes susceptibility in community dwelling han elders carrying the apolipoprotein E 3/3 genotype. *PLoS One.* 11(3), e0151336 (2016).
21. Nasreddine, Z. S. et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53(4), 695–699 (2005).
22. Kay, S. R., Fiszbein, A. & Opler, L. A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13(2), 261–276 (1987).
23. Lin, X. et al. Screening for depression and anxiety among older Chinese immigrants living in Western countries: The use of the Geriatric Depression Scale (GDS) and the Geriatric Anxiety Inventory (GAI). *Asia Pac. Psychiatry.* 8(1), 32–43 (2016).
24. Donohoo, G. G., Salomäki, A., Lehtimäki, T., Pullki, K. & Kairisto, V. Rapid identification of apolipoprotein E genotypes by multiplex amplification refractory mutation system PCR and capillary gel electrophoresis. *Clin. Chem.* 45(1), 143–146 (1999).
25. Tian, Y. et al. Obesity in Chinese patients with chronic schizophrenia: Prevalence, clinical correlates and relationship with cognitive deficits. *Schizophr. Res.* 215, 270–276 (2020).
26. Wang, J. et al. The prevalence and independent influencing factors of obesity and underweight in patients with schizophrenia: A multicentre cross-sectional study. *Eat Weight Disord.* 26, 1365–1374 (2020).
27. Annamalai, A., Kosur, U. & Tek, C. Prevalence of obesity and diabetes in patients with schizophrenia. *World J. Diabetes.* 8(8), 390–396 (2017).
28. Subramaniam, M. et al. Body mass index, obesity, and psychopathology in patients with schizophrenia. *J. Clin. Psychopharmacol.* 34(1), 40–46 (2014).
29. Alberti, K. G., Zimmet, P. & Shaw, J. Metabolic syndrome—A new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet. Med.* 23(5), 469–480 (2006).
30. Mitchell, A. J. et al. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—A systematic review and meta-analysis. *Schizophr. Res.* 39(2), 306–318 (2013).
31. Höng, G. J. Schizophrenia and antipsychotics: Metabolic alterations and therapeutic effectivity. *Vertex* 29(138), 139–147 (2018).
32. Scheepers-Hoeks, A. M. et al. Schizophrenia and antipsychotics associated with the metabolic syndrome. An overview. *Tijdschr. Psychiatr.* 50(10), 645–654 (2008).
33. Monte Leone, P., Martiadi, V. & Maj, M. Management of schizophrenia with obesity, metabolic, and endocrinological disorders. *Psychiatr. Clin. N. Am.* 32(4), 775–794 (2009).
34. Eckel, R. H., Alberti, K. G., Grundy, S. M. & Zimmet, P. Z. The metabolic syndrome. *Lancet* 375(9710), 181–188 (2010).
35. Morea, M., Miu, N., Morea, V. F. & Cornean, R. Maternal obesity—A risk factor for metabolic syndrome in children. *Chij. Med. (66), 259–265 (2013).
36. Gepstein, V. & Weiss, R. Obesity as the main risk factor for metabolic syndrome in children. *Front. Endocrinol. (Lausanne).* 10, 568 (2019).
37. Ma, X. et al. HTR2C polymorphisms, olanzapine-induced weight gain and antipsychotic-induced metabolic syndrome in schizophrenia patients: A meta-analysis. *Int. J. Psychiatry Clin. Pract.* 18(4), 229–242 (2014).
38. Mitchell, A. J., Delaffon, V., Vancampfort, D., Correll, C. U. & De Hert, M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: Systematic review and meta-analysis of screening practices. *Psychol. Med.* 42(1), 125–147 (2012).
39. Mitchell, A. J., Vancampfort, D., De Herdt, A., Yu, W. & De Hert, M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr. Bull.* 39(2), 295–305 (2013).
40. Utermann, G., Kindermann, I., Kaffarnik, H. & Steinmetz, A. Apolipoprotein E phenotypes and hyperlipidemia. *Hum. Genet.* 65(3), 232–236 (1984).
41. Rodrigues, M. O. et al. APOE genotypes and dyslipidemias in a sample of the Portuguese population. *Clin. Chem. Lab. Med.* 43(9), 907–912 (2005).
42. Zhang, X. et al. Study on apoE gene polymorphism in Chinese type II b hyperlipidemia. *Hua Xi Yi Ke Da Xue Xue Bao* 32(2), 179–182 (2001).
43. Rashid, N. A. et al. Unraveling the relationship between obesity, schizophrenia and cognition. *Schizophr. Res.* 151(1–3), 107–112 (2013).
44. Depp, C. A. et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. *Bipolar Disord.* 16(4), 422–431 (2014).
45. Janney, C. A. et al. Sedentary behavior and psychiatric symptoms in overweight and obese adults with schizophrenia and schizoaffective disorders (WAIST Study). *Schizophr. Res.* 145(1–3), 63–68 (2013).
46. Storch Jakobsen, A. et al. Associations between clinical and psychosocial factors and metabolic and cardiovascular risk factors in overweight patients with schizophrenia spectrum disorders—Baseline and two-years findings from the CHANGE trial. *Schizophr. Res.* 199, 96–102 (2018).
47. Tsai, S. Y. et al. Body mass index, residual psychotic symptoms, and inflammation associated with brain volume reduction in older patients with schizophrenia. *Int. J. Geriatri. Psychiatry.* 35(7), 728–736 (2020).
48. MacKenzie, N. E. et al. Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. *Front. Psychiatry.* 9, 622 (2018).
49. Spangaro, M., Mazza, E., Poletti, S., Cavallaro, R. & Benedetti, F. Obesity influences white matter integrity in schizophrenia. *PsychoNeuroendocrinology* 97, 135–142 (2018).
50. Kao, A. C., Burnet, P. W. J. & Lennox, B. R. Can prebiotics assist in the management of cognition and weight gain in schizophrenia? *PsychoNeuroendocrinology* 95, 179–185 (2018).
51. Andy, M., Huige, L. & Ning, X. The role of Sirtuin1 in regulating endothelial function, arterial remodeling and vascular aging. *Front. Physiol.* 10, 1173 (2019).
52. Kishi, A. T. et al. SIRT1 gene, schizophrenia and bipolar disorder in the Japanese population: An association study. *Genes Brain Behav.* 10(3), 257–263 (2011).
53. Wang, Y. et al. Association between Silent Information Regulator 1 (SIRT1) gene polymorphisms and schizophrenia in a Chinese Han population. *Psychiatry Res.* 225(3), 744–745 (2015).
54. Shaday, M. *et al.* SIRT1 is essential for normal cognitive function and synaptic plasticity. *J. Neurosci.* **30**(29), 9695–9707 (2010).
55. Schug, T. T. & Li, X. Sirtuin 1 in lipid metabolism and obesity. *Ann. Med.* **43**(3), 196–211 (2011).
56. Lima, D. *et al.* Electrochemical detection of specific interactions between apolipoprotein E isoforms and DNA sequences related to Alzheimer's disease. *Bioelectrochemistry* **133**, 107447 (2020).
57. Campagna, J. *et al.* A small molecule ApoE4-targeted therapeutic candidate that normalizes sirtuin 1 levels and improves cognition in an Alzheimer's disease mouse model. *Sci. Rep.* **8**(1), 17574 (2018).
58. Theendakara, V. *et al.* Neuroprotective sirtuin ratio reversed by ApoE4. *Proc. Natl. Acad. Sci. U. S. A.* **110**(45), 18303–18308 (2013).
59. Maria, T. *et al.* Environment and gene association with obesity and their impact on neurodegenerative and neurodevelopmental diseases. *Front. Neurosci.* **28**(14), 863 (2020).

**Author contributions**
W.L. contributed to the study concept and design. R.L., F.L. and X.Z. collected this data, G.L. and S.X. provided project funding. All authors read and approved the final manuscript.

**Funding**
This work was supported by grants from the Clinical research center project of Shanghai Mental Health Center (CRC2017ZD02), the Cultivation of Multidisciplinary Interdisciplinary Project in Shanghai Jiaotong University (YG2019QNA10), curriculum reform of Medical College of Shanghai Jiaotong University, the Feixiang Program of Shanghai Mental Health Center (2020-FX-03), Shanghai Clinical Research Center for Mental Health (19MC1911100) and Clinical study on the treatment of senile depression by tiaoqi jieyu acupuncture (18401970602).

**Competing interests**
The authors declare no competing interests.

**Additional information**

**Correspondence** and requests for materials should be addressed to G.L. or S.X.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

[Open Access](http://creativecommons.org/licenses/by/4.0/) This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/).