中文摘要

重度抑郁症与常见代谢性疾病及消化系统疾病因果关联的孟德尔随机化研究

目的：

重度抑郁症（Major depressive disorder，MDD）是一种复杂且常见的精神疾病，对患者的生活质量产生严重影响。近年来，MDD 的患病率逐渐升高，而且还常合并有其他疾患，其中包括常见的代谢性疾病和消化系统疾病。因此，评估 MDD 是否是常见代谢性疾病和消化系统疾病的风险因素对这些疾病的预防具有积极意义。

方法：

我们在 GWAS Catalog 和 Psychiatric Genomics Consortium 平台以"major depressive disorder"为关键词查询并下载当前可公开获取的 MDD 全基因组关联研究（Genome-Wide Association Studies，GWAS）数据，在 Linux 操作系统中，使用 metal 软件，对 MDD GWAS 进行荟萃分析。对荟萃分析得到的 SNPs 进行 P 值<$5×10^{-8}$ 以及去除连锁不平衡筛选，筛选得到的 SNPs 作为本孟德尔随机化（Mendelian randomization，MR）研究的工具变量（Instrumental Variables，IVs）。代谢性疾病和消化系统疾病的 GWAS 数据来自 MR-base 平台。本研究分别使用 MDD 对不同数据库来源的代谢性疾病以及消化系统疾病进行第一次探索性 MR 分析和第二次验证性 MR 分析，同时对 IVs 的有效性进行敏感性分析并评估 SNPs 及 MR 研究的统计效力。为了检查暴露和结局之间是否存在反向因果关联的情况，我们以代谢性疾病和消化系统疾病分别作为暴露，以 MDD 为结局进行 MR 分析，以确定代谢性疾病及消化系统疾病是否是 MDD 的风险因素。

结果：

1.MDD 对常见代谢性疾病的因果关系评估

荟萃分析后共筛选出 107 个 SNPs 作为 MDD 的 IVs。在探索性分析中，MDD 与肥胖（P=0.001）、2 型糖尿病（Type 2 diabetes，T2D）（P=0.003）、高

血压（Hypertension，HTN）（*P*=0.038）和高脂血症（*P*=0.002）之间呈正向因果关联，与痛风（*P*=0.081）之间无关联。其中 MDD 与 HTN、T2D、高脂血症的 MR 统计效力为 100%，而 MDD 与痛风的 MR 统计效力值仅为 5%，真实性较低。敏感性分析结果显示 MDD 与肥胖以及 T2D 的分析中存在异质性，但是在去除离群 SNP 之后，MDD 与 T2D 之间仍然呈正向因果关联。在验证性分析中，本研究证实了探索性分析得到的结果，即 MDD 与肥胖（*P*<0.001）、T2D（*P*=0.001）、HTN（*P*=0.017）和高脂血症（*P*=0.031）在正向因果关联，MDD 与痛风（*P*=0.892）之间无关联，但统计效力值为 47%，真实性较低。

2.MDD 对常见消化系统疾病的因果关系评估

我们以荟萃分析后筛选得到的 107 个 SNPs 作为 MDD 的 IVs。在探索性分析中，MDD 与慢性胃炎（*P*<0.001）、幽门螺旋杆菌感染（*P* <0.001）、食管裂孔疝（*P*<0.001）、肠易激综合征（Irritable bowel syndrome，IBS）（*P*<0.001）、胃食管反流病（Gastroesophageal reflux disease，GERD）（*P*<0.001）和食管炎（*P*<0.001）之间呈正向因果关联，其中 MDD 与慢性胃炎、GERD 和食管炎的 MR 统计效力达到了 100%。所用 IVs 不存在异质性和水平多效性，说明结果是稳健的。验证性分析结果证实，MDD 与 IBS（*P*=0.004）、GERD（*P* < 0.001）以及食管炎（*P*=0.027）之间呈正向因果关联，它们的统计效力值为 100%。MDD 与慢性胃炎（*P*=0.860）之间不存在因果关联，但其 MR 统计效力值为 5%，真实性较低。由于缺乏食管裂孔疝和幽门螺旋杆菌感染的 GWAS 数据，我们未能进行相关验证性分析。

3.常见代谢性疾病对 MDD 的因果关系评估

我们以常见代谢性疾病为暴露，MDD 为结局进行常见代谢性疾病对 MDD 因果关系的MR分析。结果表明HTN与MDD之间存在正向因果关联（*P*=0.005），敏感性分析显示存在异质性，但去除离群 SNP 后，其因果关联仍然显著（*P*=0.004），该分析的 MR 统计效力值为 100%，说明了该 MR 分析结果的真实性。其他代谢性疾病如肥胖、T2D、高脂血症和痛风与 MDD 之间未发现存在因果关联。

4.常见消化系统疾病对 MDD 的因果关系评估

我们以常见消化系统疾病为暴露，MDD 为结局进行常见消化系统疾病对 MDD 因果关系的 MR 分析。由于缺少有效的消化系统疾病 IVs，未能进行以消化系统疾病为暴 MDD 为结局的因果推断分析。

结论：

（1）MDD 会增加 HTN、肥胖、高脂血症的患病风险，其中 MDD 与 HTN 之间呈双向因果关联。（2）MDD 会增加慢性胃炎、IBS、食管裂孔疝的患病风险。

关键词：

孟德尔随机化研究，重度抑郁症，代谢性疾病，消化系统疾病

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　　论文级别：■硕士 □博士

　　学科专业：　遗传学

　　论文题目：　重度抑郁症与常见代谢性疾病及消化系统疾病因果关联的孟德尔随机化研究

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Abstract

A Mendelian randomization study on the causal association between major depressive disorder and common metabolic diseases and digestive system diseases

Objective：

Major depressive disorder (MDD) is a complex and common mental illness that seriously affects the quality of life of patients. In recent years, the prevalence of MDD has gradually increased, and it is often associated with other diseases, including common metabolic diseases and digestive system diseases. Whether MDD is a risk factor for metabolic diseases and digestive system diseases has positive significance for the prevention and treatment of these diseases.

Methods：

We searched and downloaded the currently publicly available MDD Genome-Wide Association Studies (GWAS) data on the GWAS Catalog and Psychiatric Genomics Consortium platforms with the keyword "major depressive disorder". In the Linux operating system, we used metal software to conduct meta-analysis on MDD GWAS. The SNPs obtained by the meta-analysis were screened with a P value $<5\times10^{-8}$ and linkage disequilibrium removed, and the screened SNPs were used as instrumental variables (IVs) in this Mendelian randomization (MR) study. The GWAS data of metabolic diseases and digestive system diseases come from the MR-base platform. In this study, MDD was used to conduct the first exploratory MR analysis and the second confirmatory MR analysis on metabolic diseases and digestive system diseases from different database sources. At the same time, the sensitivity analysis of the effectiveness of IVs and the statistical power of SNPs and MR studies were evaluated. In order to check whether there is a reverse causal relationship between exposure and outcome, we used metabolic diseases and digestive system diseases as exposures and MDD as the

outcome to conduct MR analysis to determine whether metabolic diseases and digestive system diseases are MDD risk factors.

Result：

1. MDD causality assessment for common metabolic diseases

A total of 107 SNPs were screened out as IVs of MDD after meta-analysis. In exploratory analysis, there was a positive causal association between MDD and obesity (P=0.001), type 2 diabetes (T2D) (P=0.003), hypertension (HTN) (P=0.038), hyperlipidemia (P=0.002), and between MDD and gout (P=0.081) there is no correlation. Among them, the statistical power of MDD and HTN, T2D, hyperlipidemia is 100%, while the statistical power of MDD and gout is only 5%, lack of authenticity. Sensitivity analysis revealed heterogeneity in the analysis of MDD and obesity as well as T2D, but after removal of outlier SNPs, there was still a positive causal association between MDD and T2D. In the confirmatory analysis, this study confirmed the results obtained in the exploratory analysis, MDD and obesity (P<0.001), T2D (P=0.001), HTN (P=0.017), hyperlipidemia (P=0.031) in a positive causal relationship. There was no association between MDD and gout (P=0.892), but with 47% power, lack of authenticity.

2. MDD causal assessment of common digestive system diseases

At this stage, 107 SNPs screened after meta-analysis were used as IVs of MDD. In exploratory analysis, MDD was associated with chronic gastritis (P<0.001), Helicobacter pylori infection (P<0.001), hiatal hernia (P<0.001), irritable bowel syndrome (IBS) (P<0.001), gastroesophageal reflux disease (GERD) (P<0.001) and esophagitis (P<0.001) showed a positive causal association, and the MR statistical power of MDD and chronic gastritis, GERD and esophagitis reached 100%. Confirmatory analysis results confirmed positive causal associations between MDD and IBS (P=0.004), GERD (P<0.001), esophagitis (P=0.027), with 100% MR statistical power. There was no heterogeneity and horizontal pleiotropy among the IVs used. There was no causal association between MDD and chronic gastritis (P=0.860), but its MR statistical power was 5%, which was lack of authenticity. During to lack of GWAS

data on hiatal hernia and Helicobacter pylori, we were unable to perform a confirmatory analysis.

3. Causality assessment of common metabolic diseases on MDD

We took common metabolic diseases as exposure and MDD as outcome to conduct MR analysis of the causal relationship between common metabolic diseases and MDD. The results showed that there was a positive causal association between HTN and MDD (P=0.005), and the sensitivity analysis showed that there was heterogeneity, but after removing the outlier SNP, the causal association was still significant (P=0.004), the MR statistical power of the analysis is 100%, indicating the authenticity of the MR analysis results. No causal association was found between other metabolic diseases such as obesity, T2D, hyperlipidemia, gout and MDD.

4.Causality assessment of common digestive system diseases on MDD

We took common digestive system diseases as exposure and MDD as outcome to conduct MR analysis of the causal relationship between common digestive system diseases and MDD. Due to the lack of valid digestive system disease IVs, causal inference analysis with digestive system disease as the exposure and MDD as the outcome could not be performed.

Conclusion:

(1) MDD can increase the risk of HTN, obesity, and hyperlipidemia, and there is a bidirectional causal relationship between MDD and HTN. (2) MDD increases the risk of chronic gastritis, IBS, and hiatal hernia.

Key words:

Mendelian randomization studies, major depressive disorder, metabolic disease, digestive system disease

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英文缩略词表

英文缩写	英文全称	中文全称
AA	Atypical antipsychotics	非典型抗精神病药
CI	Confidence interval	置信区间
DBP	Diastolic pressure	舒张压
DM	Diabetes mellitus	糖尿病
EAF	Effect allele frequency	等位基因频率
GERD	Gastroesophageal reflux disease	胃食管反流病
GUGC	Global Urate Genetics Consortium	全球尿酸盐遗传学联合会
GWAS	Genome wide association study	全基因组关联研究
HTN	Hypertension	高血压
IBS	Irritable bowel syndrome	肠易激综合征
IVs	Instrumental Variables	工具变量
LD	Linkage disequilibrium	连锁不平衡
MDD	Major depressive disorder	重度抑郁症
MR	Mendelian Randomization	孟德尔随机化
OR	Odds ratio	风险比
PGC	Psychiatric Genomics Consortium	精神病学基因组学联盟
SBP	Systolic blood pressure	收缩压
SE	Standard error	标准误
SNPs	single nucleotide polymorphisms，	单核苷酸多态性
T1D	Type 1 diabetes	1 型糖尿病
T2D	Type 2 diabetes	2 型糖尿病
TCA	Tricyclic antidepressants	三环类抗抑郁药
UKB	UK Biobank	英国生物银行
WHO	World Health Organization	世界卫生组织

引 言

重度抑郁症是一种复杂且常见的精神疾病，在世界范围内每年的发病率约为 4.4%。作为一种慢性疾病，重度抑郁症不仅给患者的心理带来了沉重负担，还常伴有一些常见代谢性疾病和消化系统疾病发生。

有多项观察性研究表明，重度抑郁症可能是一些常见代谢性疾病以及消化系统疾病的风险因素。通常观察性研究只能建立暴露与结局之间的关联，无法准确证明两者之间的因果关联，且不能排除混杂因素对因果推断的影响。因此重度抑郁症与常见代谢性疾病以及消化系统疾病之间是否存在因果关联需要进一步研究。

本研究采用孟德尔随机化方法确定重度抑郁症与代谢性疾病以及消化系统疾病之间的因果关联，为重度抑郁症患者代谢性疾病和消化系统疾病的预防提供依据。

第 1 章 文献综述

1.1 抑郁症简介

根据国际疾病分类（International Classification of Diseases，ICD）第十版（ICD-10），抑郁症的诊断标准为情绪低落、精力下降、活动减少、注意力降低、食欲下降、睡眠障碍、自信降低等症状。根据症状的数量和严重程度，抑郁症可分为轻度抑郁（两种或三种）、中度抑郁症（四种及以上）及重度抑郁。重度抑郁症（Major depressive disorder ，MDD）患者除了经常出现以上症状外，还常伴有自杀念头[1]。目前，由于缺乏特定的生物标志物用于 MDD 的诊断，研究人员对 MDD 的诊断方法不同，例如调查问卷、自我报告等，他们也常将 MDD 简称为抑郁症[2]。

世界心理健康调查估计 MDD 的年发病率为 4.4% ，终生患病率约为 10% - 15%[3]。随着社会经济的不断发展，生活节奏的加快，社会竞争日益激烈，人们的心理压力逐渐增大，MDD 的发病率逐年上升。MDD 不仅会严重影响患者的心理状况和生活质量，而且给家庭和社会带来了沉重的精神和经济负担[4]。2008 年世界卫生组织（World Health Organization， WHO）将 MDD 列为全球疾病负担的第三大原因，并预计到 2030 年 MDD 将位居第一[5]。目前，全球约有 3 亿人患 MDD，MDD 患者常伴有高比例的合并症，比如糖尿病（Diabetes mellitus ， DM）、胃食管反流病（Gastroesophageal reflux disease，GERD）、慢性阻塞性肺病和冠状动脉疾病等医学合并症[6]，这些都加重了 MDD 患者自杀的风险。

1.2 MDD 与常见代谢性疾病的相关性

代谢性疾病是一类疾病的总称，是指由我们身体中的物质，如脂肪、糖、蛋白质、嘌呤等代谢异常引起的营养物质累积或缺乏而引起的疾病，主要包括 DM、肥胖、高血压（Hypertension ， HTN）、高脂血症和痛风等。近年来观察到代谢性疾病的发病率呈上升趋势，已成为全球主要的公共卫生问题[7, 8]。

DM 是一种由于机体无法有效产生或利用胰岛素而引起血糖升高的慢性代