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Evaluating the causal relationship of Levo-carnitine and risk of schizophrenia: a bidirectional two-sample mendelian randomization study

Haoyuan Qiu[1], Zicheng Zhong[1], Tianxing Wu[2], Haoran Hu[1], Meijuan Zhou[3*] and Zhijun Feng[4*]

Abstract

Background Schizophrenia is a debilitating mental disorder affecting about 1% of the global population, characterized by significant cognitive impairments and a strong hereditary component. Carnitine, particularly Levo-carnitine and its derivatives, plays a crucial role in cellular metabolism and mitochondrial function, with evidence suggesting a link between levo-carnitine deficiency and schizophrenia pathology. This study aims to investigate the causal relationship between different subtypes of levo-carnitine and the susceptibility to schizophrenia using Mendelian randomization analysis.

Methods Forward Mendelian randomization analysis was conducted using levo-carnitine and its derivatives as exposure and schizophrenia as the outcome. Candidate data were obtained from the Open-GWAS database. Instrumental variables were identified as single nucleotide polymorphisms closely associated with exposure and harmonized with the outcome data after removing confounders and outliers. Mendelian randomization analysis was performed using inverse variance weighting as the primary approach, and sensitivity analysis was conducted to assess the reliability and robustness of the results. Finally, a reverse Mendelian randomization analysis was carried out using the same analytical procedures.

Results The Mendelian randomization results indicate a significant negative causal relationship between isovaleryl-levo-carnitine and schizophrenia ($P < 0.05$), but no significant associations in other groups ($P > 0.05$). Additionally, the reverse Mendelian randomization analysis did not identify any causal relationship between schizophrenia and levo-carnitine related exposures ($P > 0.05$). Sensitivity analyses, including pleiotropy and heterogeneity analysis, did not reveal any potential bias in the Mendelian randomization results ($P > 0.05$).

Conclusion The results suggest that elevated levels of isovaleryl-levo-carnitine may potentially mitigate the risk of developing schizophrenia, highlighting the prospective therapeutic and preventive implications of isovaleryl-levo-carnitine in the clinical management of schizophrenia.

Keyword Schizophrenia; levo-carnitine; carnitine; mendelian randomization

*Correspondence:
Meijuan Zhou
lkzmj@smu.edu.cn
Zhijun Feng
fengzhj18@sina.com
Full list of author information is available at the end of the article

Background

Schizophrenia (SZ) is a highly debilitating mental disorder, affecting approximately 1% of the global population, and is widely recognized as the most severe of all mental illnesses [1, 2]. The disorder is marked by a spectrum of symptoms, including hallucinations (commonly auditory), delusions (fixed false beliefs), disorganized thinking, and negative symptoms such as social withdrawal and lack of motivation. SZ typically manifests in late adolescence or early adulthood, with men often experiencing an earlier onset than women [3]. This disorder has a significant hereditary component, characterized by a wide array of genetic variations, encompassing both common single nucleotide polymorphisms (SNPs) and rare mutations [4]. Recent advancements in molecular biology have identified numerous risk genes associated with SZ, providing genetic evidence that supports familial transmission. These findings underscore the crucial role of genetics in the etiology of SZ and offer compelling insights into understanding susceptibility to the disorder from a genetic variation perspective [5]. In summary, SZ is a complex disorder influenced by multiple genes, as evidenced by various genetic variants [6]. Thus, exploring the genetic origins of psychiatric disorders or identifying potential therapeutic targets through the lens of genetic variants holds significant practical implications. Despite decades of extensive research, the underlying pathological mechanisms of SZ remain incompletely understood.

The endogenous pool of carnitine consists of levo-carnitine (LC) and acylcarnitine, wherein LC serves as the active form for carnitine while acylcarnitine is a derivative state derived from LC [7, 8]. LC plays a crucial role in the β-oxidation of fatty acids within the human body [9, 10], and its synthesis occurs via biosynthesis, utilizing the amino acids lysine and methionine [11, 12]. Among the derivative states in the LC pool, acetyl-LC (ALC), propionyl-LC (PLC), and isovaleryl-LC (ILC) are three types that exhibit significant biological activity and have garnered attention. LC is ubiquitously present in the majority of cells within the human body [13], and assumes a vital role in upholding the integrity of cell membranes and exhibits specific functionalities within mitochondria [14]. Prior investigations have substantiated that an insufficiency of LC results in the enlargement of astrocytes and the expansion of mitochondria in nerve cells [15]. The presence of mitochondrial dysfunction in SZ is substantiated by a confluence of evidence derived from genetic and peripheral investigations [16]. This implies that LC may play a role in the pathological mechanisms underlying SZ, exerting an impact on the structural and energetic metabolism aspects of nerve cells. Furthermore, the study conducted by Kriisa et al. posited that impairment in LC function could potentially give rise to psychiatric disorders, including SZ [17]. In a prospective cohort study, the efficacy of olanzapine, the primary antipsychotic medication prescribed for individuals with SZ, was observed to significantly diminish the concentrations of LC metabolites in patients with SZ. Additionally, the reduction in LC metabolite levels exhibited a significant correlation with cognitive enhancement subsequent to treatment [18]. ALC is an endogenous compound that is prominently present in various bodily tissues, including muscles, the brain, and sperm. The significance and neuro-protective properties of these carnitines have been extensively validated through con-temporary scientific investigations. In light of observational research, the collective evidence substantiates the potential involvement of LC and its derivatives in the etiology, progression, and therapeutic intervention of SZ [19]. Nevertheless, the existence of a definitive causal association between the two remains uncertain.

In recent years, the employment of Mendelian randomization (MR) has facilitated the ability to deduce causal connections between modifiable environmental exposures and outcomes, thus garnering growing attention [20]. MR leverages genetic variation found in SNPs as instrumental variables (IVs) within observational contexts. By virtue of genetic variations being randomly allocated during gamete formation and being un-affected by environmental and lifestyle factors, the estimates derived from MR exhibit reduced vulnerability to confounding bias. Moreover, it is imperative that the individual's lineage genotype is established prior to examining the outcome of interest, and the measurement of genetic variants must be conducted with utmost accuracy. This meticulous approach in conducting MR analysis reduces the susceptibility to biases arising from reverse causation and measurement errors. Consequently, we have chosen to investigate the causal association between different subtypes of LC, as determined by genetic factors, and the susceptibility to SZ using a two-sample bidirectional MR analysis.

Methods

Study design

In order to assess the potential causal relationship between different derivatives of LC and SZ, a Two-sample MR analysis was conducted. This analysis was guided by three fundamental principles [21]: (1) The use of SNPs identified through genome-wide association studies (GWAS) as IVs for the exposure variable; (2) Ensuring that the IVs are not associated with confounding factors; (3) Confirming that the IVs solely influence the risk of the outcome through their association with the exposure, without exerting a direct impact on the outcome itself. The forward MR analysis primarily aimed to ex-amine

the correlation between LC and its derivatives as the exposure, and SZ as the primary outcome. Conversely, in reverse analysis, SZ was considered as the exposure variable, while LC and its derivatives were regarded as the outcome variables (Fig. 1). This study was conducted in accordance with the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology Mendelian randomization (STROBE-MR) [22].

Data sources

The data for this MR analysis were sourced from the OpenGWAS Project [23, 24]. Our selection criteria included datasets representing European populations, with substantial sample sizes and detailed information on LC and its derivatives as exposure variables, with SZ as the outcome. In a previous meta-analysis by Sakaue et al., a cohort comprising 6,334 cases and 445,120 controls was chosen as the SZ dataset [25]. This study utilized nuclear magnetic resonance spectroscopy and mass spectrometry to ensure precise metabolite quantification across different populations. Additionally, we used data from Shin et al., who analyzed samples from 7,824 adults in two European population studies using liquid chromatography and gas chromatography coupled with tandem mass spectrometry (LC–MS/MS and GC–MS/MS) to form the LC dataset. Detailed information on each dataset is provided in Table S1 [26].

For external validation, we incorporated two additional datasets. The first was a Finnish cohort with a sample size of 224,737, including ILC data, which allowed us to replicate our primary findings using a two-sample MR analysis [27]. The second dataset was from the Canadian Longitudinal Study on Aging, consisting of 8,299 individuals of European ancestry [28]. This cohort was genotyped genome-wide, and plasma metabolites were quantified using ultrahigh performance liquid chromatography–tandem mass spectrometry. These original GWAS and metabolomics studies are foundational to our MR analysis, providing the IVs necessary for exploring causal relationships. More information is available on the OpenGWAS website at "https://gwas.mrcieu.ac.uk/about/".

Identified IVs

Firstly, IVs were selected from the exposure data using a quality control procedure. The "TwoSampleMR" R package in the R software was utilized to extract IVs associated with exposure by setting parameters (P = 1e-5,

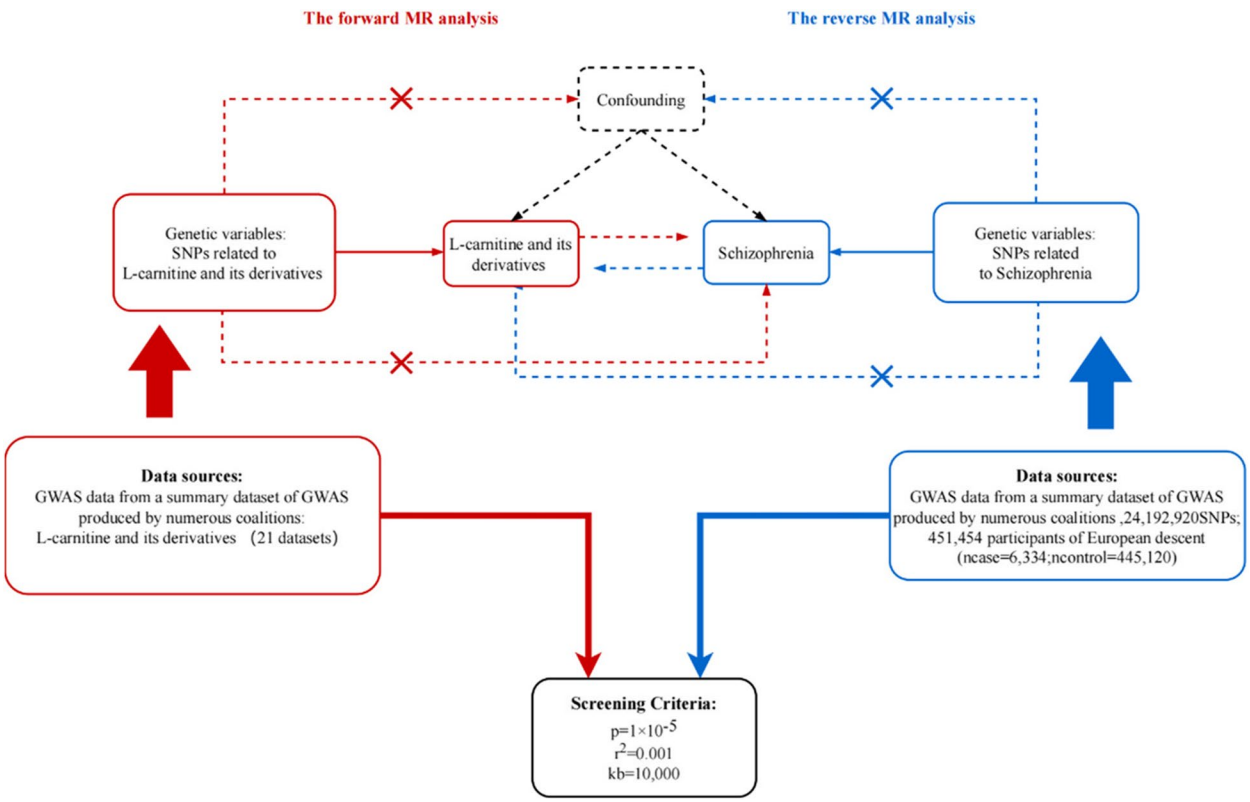

Fig. 1 Principles of bidirectional mendelian randomization study and our study design. MR, Mendelian randomization; GWAS, genome-wide association studies. p, r2, and kb represent the parameters in the "TwoSampleMR" R package

clump = True, r2 = 0.001, kb = 10000) [23, 29]. Due to the inherent uncertainty regarding the causality of SZ, potential confounding variables related to exposure-associated IVs were not adequately controlled for, and we employed a filtration process to eliminate and exclude confounding variables specifically linked to SZ utilizing "phenoscanner" R package [30]. If an IV is significantly associated with SZ related diseases or phenotypes (e.g., depression, anxiety disorder, affective disorder), it is identified as a potential confounder and excluded. Hence, the efficacy of IVs was assessed by examining the F statistics, which quantifies the level of association between the SNPs and the exposure. Subsequently, relevant information pertaining to IVs closely aligned with exposure was extracted from the outcome data set. After harmonized the extracted data, a screening process was implemented to exclude IVs that were closely associated with outcomes ($P < 5e\text{-}8$) from the data. In order to clarify the potential impact of outliers in IVs on the MR analysis results, the "MR-PRSSO" package [31] was utilized to verify the presence of outliers in the harmonized data and subsequently eliminate them. All the IVs selected based on the above criteria are stored in Table S2. Additionally, we excluded IVs that exhibited anomalies during the analysis or failed the Steiger analysis. The details of all IVs included in the final MR analysis are presented in Table S3.

MR analysis

After completing the initial procedures, we employed five methodologies—MR-Egger [32], weighted median [33], IVW [34], simple mode [35], and weighted mode [35]—to evaluate the overall effect outcomes in our MR analyses. Significant results were determined by an IVW method P-value of less than 0.05, with consistent b-values across supplementary methods. IVW combines the effects of multiple IVs by weighting them according to their inverse variance, reducing the influence of less precise estimates and providing a more accurate overall causal effect [34]. This method is particularly effective when all IVs are valid. Using the "TwoSampleMR" R package, we calculated the odds ratios (OR) and their 95% confidence intervals (CI) for each direction of analysis to assess the causal effects revealed by the MR analysis.

Sensitivity analysis

Sensitivity analysis incorporates the examination of heterogeneity and pleiotropy, as well as the assessment of the impact of an individual SNP on the overall outcomes of MR analysis. Heterogeneity was evaluated using MR-Egger methods, specifically by implementing the Q-test [23]. In instances where heterogeneity was detected, a random effects model was utilized to reevaluate the magnitude of the effect. Moreover, the representation of heterogeneity was achieved by employing Scatter plot and Funnel plot techniques. Additionally, the presence of horizontal pleiotropy in the IVs was assessed using the Egger intercept method. Furthermore, the influence of excluding a single SNP on the results of the MR analysis was examined through the application of the leave-one-out method. To verify whether the statistical power of our MR analysis meets the requirements, we used the mRnd("https://shiny.cnsgenomics.com/mRnd/") method to calculate it and found that the statistical power reached 0.94, thereby demonstrating the reliability of our study.

Evaluation of sample overlap bias

In order to further substantiate the influence of sample overlap on the outcomes of MR analysis, we employed the "mrSampleOverlap" R package to assess the bias and Type I error associated with varying levels of sample overlap rates. If the findings of this examination demonstrate that the bias and Type I error persist at a relatively consistent level despite an increase in the repetition rate of samples, it indicates the relative robustness of the MR analysis results.

Validation MR analysis

To ensure the accuracy and reliability of our analysis, we conducted three additional validation experiments using different datasets for ILC, with outcome data substituted from a Finnish cohort. The ILC data were initially sourced from the UK Biobank. The IVs related to the exposure were selected using the same criteria as in our primary analysis. After removing confounding factors, a two-sample MR analysis was performed. Additionally, corresponding sensitivity analyses were conducted to further validate the robustness of our findings.

Results

Forward analysis

Forward MR analysis

Based on the findings from the forward MR analysis, it is apparent that LC and its derivatives demonstrate inconsistent causal effects on SZ, as indicated in Table 1. Among the results from three primary derivatives of LC (ALC, PLC, ILC), only ILC exhibits a negative causal relationship with SZ (Table 1, OR = 0.435, 95% CI: 0.247–0.765, PIVW = 0.004). Conversely, the remaining substances do not exhibit a significant causal relationship with SZ (Table 1, PIVW > 0.05). The detailed results of the Forward MR analysis are presented in Table S4.

Forward sensitivity analysis

The sensitivity analysis results provided confirmation that there was no statistically significant presence of

Table 1 Forward mendelian randomization results of causality of LC and its derivatives on schizophrenia

Exposure	N_{SNP}	IVW		MR Egger		Weighted median		Simple mode		Weighted mode	
		OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*
Levo-carnitine	16	0.647	0.633	0.223	0.437	0.402	0.455	0.528	0.715	0.425	0.518
Palmitoyl-levo-carnitine	9	0.932	0.884	0.879	0.916	0.822	0.773	0.572	0.593	0.76	0.712
Acetyl-levo-carnitine	18	0.789	0.568	1.645	0.656	0.776	0.654	0.565	0.495	0.762	0.704
Isovaleryl-levo-carnitine*	14	0.435	0.004	0.562	0.241	0.502	0.09	0.333	0.086	0.463	0.072
2-methylbutyroyl-levo-carnitine	24	1.56	0.319	0.707	0.806	1.283	0.71	1.56	0.319	0.761	0.495
2-tetradecenoyl-levo-carnitine	19	0.797	0.3	0.784	0.41	0.825	0.582	0.825	0.582	0.825	0.582
Butyryl-levo-carnitine	24	0.887	0.39	1.035	0.614	0.873	0.467	0.873	0.467	0.873	0.467
Hexanoyl-levo-carnitine	16	0.687	0.17	0.739	0.659	0.472	0.096	0.472	0.096	0.472	0.096
Octanoyl-levo-carnitine	15	0.929	0.816	0.426	0.057	0.59	0.141	0.59	0.141	0.59	0.141
Glutaroyl-levo-carnitine	31	0.736	0.273	0.255	0.634	0.377	0.145	0.377	0.145	0.377	0.145
Lauryl-levo-carnitine	13	0.769	0.434	1.38	0.767	0.931	0.87	0.931	0.87	0.931	0.87
Propionyl-levo-carnitine	29	0.681	0.403	0.398	0.355	0.442	0.173	0.442	0.173	0.442	0.173
Decanoyl-levo-carnitine	14	0.658	0.122	0.336	0.04	0.455	0.023	0.493	0.103	0.493	0.103
Oleoyl-levo-carnitine	11	1.227	0.693	0.303	0.409	0.712	0.587	0.712	0.587	0.712	0.587
Cis-4-decenoyl-levo-carnitine	9	0.477	0.043	0.596	0.491	0.42	0.041	0.42	0.041	0.42	0.041
Isobutyryl-levo-carnitine	10	1.097	0.761	0.731	0.627	0.753	0.461	0.753	0.461	0.753	0.461
X-13431-nonanoyl-levo-carnitine	3	1.002	0.896	0.996	0.939	1.001	0.979	1.001	0.979	1.001	0.979
Hydroxyisovaleroyl-levo-carnitine	8	0.693	0.33	0.654	0.544	0.77	0.576	0.77	0.576	0.77	0.576
Succinyl-levo-carnitine	39	1.004	0.993	3.571	0.207	1.782	0.338	1.782	0.338	1.782	0.338
3-dehydro-levo-carnitine	21	0.94	0.882	0.656	0.741	0.888	0.842	0.888	0.842	0.888	0.842
Stearoyl-levo-carnitine	3	1.004	0.839	1.001	0.997	1.003	0.903	1.003	0.903	1.003	0.903

N_{SNP} number of single nucleotide polymorphisms, IVW inverse-variance weighted, OR odds ratio

* MR analysis revealed that Isovalerylcarnitine has a negative causal relationship with schizophrenia

pleiotropy or heterogeneity in the IVs associated with each groups during the forward MR analysis process (Table s4, $P > 0.05$). Furthermore, the scatter plot distributions indicated potential linear associations within all three analysis groups (Fig. 2A-C). Moreover, the absence of conspicuous abnormal SNP distributions was also verified through examination of the funnel plot (Fig. 3A-C). The varying impact of individual IVs on SZ is evident

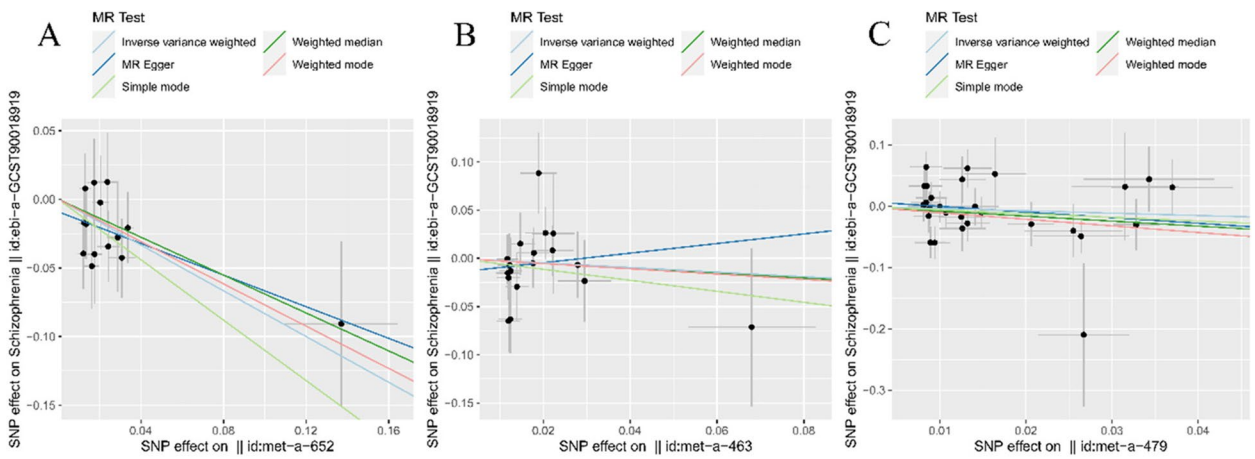

Fig. 2 Scatter plots of mendelian randomization analysis for representative acylcarnitine types (exposure) and schizophrenia (outcome). **A** Scatter plot of the causal relationship between ILC and schizophrenia. **B** Scatter plot of the causal relationship between ALC and schizophrenia. **C** Scatter plot of the causal relationship between PLC and schizophrenia

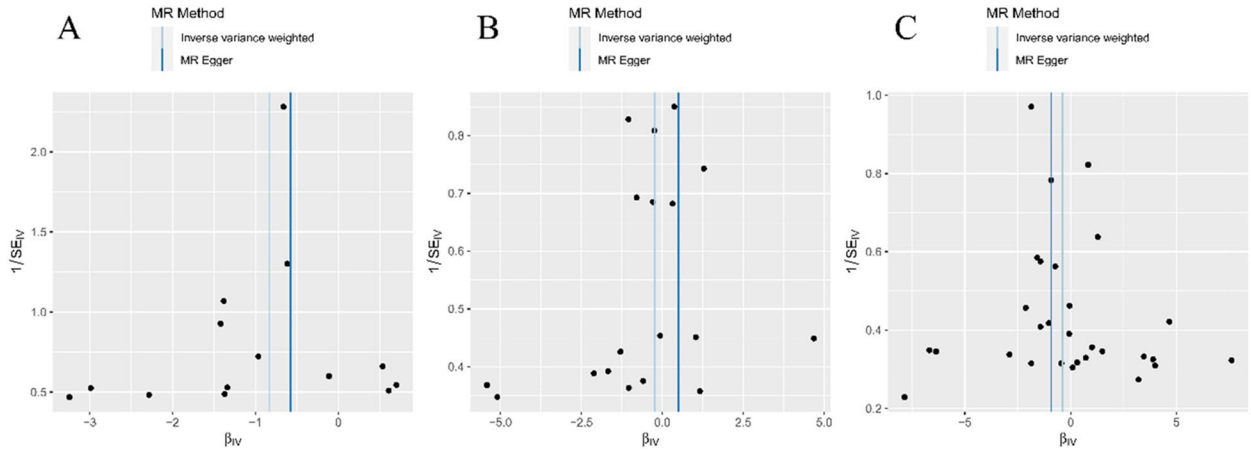

Fig. 3 Funnel plots of mendelian randomization analysis for representative acylcarnitine types (exposure) and schizophrenia (outcome). **A** Funnel plot of the causal relationship between ILC and schizophrenia. **B** Funnel plot of the causal relationship between ALC and schizophrenia. **C** Funnel plot of the causal relationship between ALC and schizophrenia

across different IVs (Supplementary Materials 1). Furthermore, employing the leave-one-method for evaluation substantiates that the influence of a single IVs on the main findings of MR analysis remains insignificant (Supplementary Materials 2). These findings collectively affirm the robustness and dependability of the analytical outcomes in the present study. To verify whether the statistical power of our MR analysis meets the requirements, we used the mRnd method to calculate it and found that the statistical power reached 0.94, thereby demonstrating the reliability of our study.

Sample overlap bias in forward analysis

The results indicated a slight increase in both bias and type I error with an in-creasing rate of sample duplication. However, the overall level remained relatively stable (Supplementary Materials 3). These findings suggest that there is no significant duplication of samples among the population included in this study, thereby reinforcing the reliability and validity of our MR analysis results.

Reverse analysis

The findings from the reverse MR analysis suggest that there is no statistically significant causal association between SZ and LC and its derivatives (Table 2, Table S3, $P > 0.05$). The sensitivity analysis results indicate that there is no significant pleiotropy among the IVs in each group (Table S5, $P > 0.05$), but they do exhibit varying levels of heterogeneity (Table S5). Furthermore, when examining different IVs, the effects of a single IV on SZ are found to be significant (Supplementary Materials 1). Nevertheless, employing the leave-one-out method for evaluation confirms that the impact of a single IV on the primary outcomes of MR analysis remains statistically insignificant (Supplementary Materials 2). Additionally, the examination of sample overlap's influence on the results of the MR analysis yielded comparable findings to the forward analysis (Supplementary Materials 3).

Table 2 Reverse mendelian randomization results of causality of schizophrenia on levo-carnitine and its derivatives

Outcome	N_{SNP}	*P*	OR	95%CI
Levo-carnitine	10	0.736	1.001	0.995–1.008
Palmitoyl-levo-carnitine	9	0.797	0.993	0.941–1.047
Acetyl-levo-carnitine	18	0.317	0.993	0.979–1.007
Isovaleryl-levo-carnitine	14	0.555	0.992	0.966–1.019
Hexanoyl-levo-carnitine	16	0.942	1.001	0.970–1.033
Butyryl-levo-carnitine	24	0.802	0.994	0.951–1.040
Propionyl-levo-carnitine	29	0.690	0.998	0.986–1.010
3-dehydro-levo-carnitine	21	0.797	1.003	0.982–1.024
Isobutyryl-levo-carnitine	10	0.779	0.995	0.964–1.028
Octanoyl-levo-carnitine	15	0.689	1.007	0.974–1.040
Decanoyl-levo-carnitine	14	0.788	1.007	0.960–1.055
Stearoyl-levo-carnitine	3	0.344	0.547	0.157–1.910
Lauryl-levo-carnitine	13	0.884	1.006	0.929–1.089
Oleoyl-levo-carnitine	11	0.880	1.002	0.981–1.023
X-13431-nonanoyl-levo-carnitine	3	0.467	1.179	0.757–1.835
2-methylbutyroyl-levo-carnitine	24	0.884	0.999	0.979–1.019
Hydroxyisovaleroyl-levo-carnitine	8	0.985	1.000	0.979–1.021
Glutaroyl-levo-carnitine	31	0.644	1.004	0.986–1.023
2-tetradecenoyl-levo-carnitine	19	0.829	1.003	0.973–1.035
Succinyl-levo-carnitine	39	0.824	0.997	0.967–1.027
Cis-4-decenoyl-levo-carnitine	9	0.619	1.008	0.977–1.040

N_{SNP} number of single nucleotide polymorphisms, *OR* odds ratio, *P* pval for inverse-variance weighted method, *CI* confidence interval

Validation MR analysis

To verify the reliability of our experimental results, we introduced external validation exposures and outcomes. The IVs used in these experiments are detailed in Tables S2 and S3. In the external validation dataset, we observed a significant negative correlation between ILC and SZ ($P_{IVW} < 0.05$). The specific results of the external validation are summarized in Table 3, with further details provided in Table S6. Additionally, all external validation experiments successfully passed our sensitivity analysis, as shown in Table S7 and Supplementary Materials 1, 2, and 3. These external validation findings further support the potential negative causal relationship between ILC and SZ.

Discussion

In this study, we employed a two-sample MR analysis to explore the bidirectional causal relationships between LC-related subtypes, their metabolite levels, and SZ. The results demonstrated a significant negative causal effect between ILC and SZ, and validation analyses across different datasets also confirmed this negative causal relationship, suggesting that higher levels of ILC may help prevent the onset of SZ. The reverse MR analysis did not show a significant causal effect between LC and SZ, indicating that carnitine and its related subtypes are not major metabolites in the progression of SZ. These findings further support the potential protective role of ILC in preventing SZ and suggest that future research could focus on ILC as a target for intervention, providing a theoretical basis for developing preventive and therapeutic strategies for SZ.

Previous research has largely focused on the general role of carnitine in neurological disorders. It's well known that individuals with SZ are prone to metabolic irregularities and bioenergetic dysfunction [1, 36]. Notably, Cao B. et al. have linked ALC to the bioenergetic abnormalities in SZ, suggesting ALC as a potential area for further study in the context of SZ [37]. Studies also found that LC and ALC can reduce neurotoxicity caused by mitochondrial dysfunction, such as uncoupling or oxidative phosphorylation inhibition [38, 39]. Another study by M. Pennisi, G. Lanza et al. explored ALC's role in dementia, showing its potential to slow cognitive decline through mechanisms like restoring cellular and synaptic function, promoting mitochondrial energy metabolism, protecting against toxins, and exerting neurotrophic effects [40]. ALC has also been tested in clinical trials as an adjunct therapy for conditions like dementia [41] and geriatric depression [42].

Research shows that nerve growth factor (NGF) significantly impacts neuron development and maintenance. J.W. Pettegrew et al. found that aged rats treated with ALC showed improvement in NGF-binding capacity in brain regions, suggesting that certain forms of LC might enhance neuron responsiveness to neurotrophic factors in older rats [43]. Some LC variants also modulate NGF activity, influence hormone levels, and regulate synaptic morphology and neurotransmitter transmission, including acetylcholine [44]. These findings suggest that specific LC subtypes can affect multiple central nervous system targets, including neurotransmitter concentrations. In child injury models, ALC has been shown to improve mitochondrial function, reduce brain swelling, and prevent tissue loss, with continued administration enhancing cerebral energy in healthy mice [41, 45, 46]. Building on these studies, our research examined the causal relationship between specific LC subtypes and SZ. We found a consistent and significant inverse correlation between ILC and SZ, supporting our hypothesis that certain LC subtypes may protect against SZ. Additionally, Zhao L. et al. found an association between reduced butyryl-LC levels and cognitive improvement in SZ patients following olanzapine monotherapy, further indicating that L-carnitine may influence cognitive function in SZ patients [18]. This finding, however, does not conflict with our results. Our study identified a potential causal relationship between elevated ILC levels and a reduction in SZ risk. While both ILC and butyryl-LC belong to the carnitine family, they are derived from different fatty acids and participate in distinct metabolic pathways, which may lead to differing, or even opposite, effects on SZ.

The therapeutic use of LC for SZ is gaining attention. For instance, some studies suggest that L-carnitine might help prevent memory impairments associated with PTSD by protecting neurons from oxidative stress, thereby improving cognitive function [47]. In animal studies, L-carnitine has shown promise in reducing fatigue and improving psychomotor function, likely due to its role in promoting fatty acid metabolism and boosting energy levels [48]. These properties make L-carnitine a

Table 3 The main data analysis and external validation results regarding the relationship between isovalery-levo-carnitine and schizophrenia (cited using the name of the first author of the original database)

Exposure	Outcome	N_{SNP}	*P*	OR	95%CI
Shin.et.al	Sakaue.et.al	14	0.004	0.435	0.247–0.765
Shin.et.al	Kurki.et.al	17	0.022	0.604	0.392–0.931
Chen.et.al	Sakaue.et.al	20	0.036	0.866	0.757–0.991
Chen.et.al	Kurki.et.al	22	0.025	0.906	0.831–0.988

N_{SNP} number of single nucleotide polymorphisms, *OR* odds ratio, *P* pval for inverse-variance weighted method, *CI* confidence interval

promising candidate for preventing and treating certain mental disorders [49]. Particularly in cases of neurodegeneration caused by trauma or stress, L-carnitine may offer protective effects by enhancing brain energy supply and reducing oxidative damage [50]. These findings suggest that LC and its derivatives have significant therapeutic potential in managing SZ.

Current research on the link between LC and psychiatric disorders has mainly focused on ALC, while the role of ILC in mental health remains underexplored. In our study, we found no causal relationship between other LC subtypes and SZ, likely due to study population limitations, which requires further investigation. However, we did identify a significant causal relationship between ILC and SZ. ILC is a biologically important compound involved in metabolism, cellular signaling, and detoxification. It has been shown to enhance calpain activity at low calcium concentrations, influencing processes like apoptosis and inflammation [13]. Preliminary research suggests that ILC may offer benefits in certain contexts, such as improving survival in specific cellular environments [51]. While the direct therapeutic use of ILC is still being studied, the broader role of other LC subtypes in brain metabolism highlights its potential significance in neuroprotection and treating neurological disorders. Therefore, more research is needed to fully understand ILC's therapeutic potential and mechanisms. Our study provides a foundation for further exploration of these relationships and potential therapeutic strategies.

The study's merits encompass the utilization of two-sample MR analysis, which, in contrast to observational studies, can effectively mitigate the influence of confounding variables and reverse causality. Leveraging publicly accessible GWAS summary statistics data, we derived advantages from a substantial sample size, thereby augmenting the accuracy of our estimations and the statistical robustness of our discoveries. This methodological framework guarantees a heightened level of result reliability.

However, several limitations of our study must be acknowledged. First, our findings are primarily applicable to populations of European ancestry. While this focus helps mitigate biases due to population stratification, the generalizability of our results to other ethnic groups remains uncertain. Second, like any Mendelian Randomization (MR) study, our analysis may be influenced by unobserved pleiotropy, potentially introducing bias. Thus, further comprehensive research involving diverse populations and varied methodological approaches is essential to validate and enhance the accuracy of our findings. In our MR analysis of various carnitines, we conducted independent analyses for each subtype to ensure the reliability of the results. We recognized that appropriate correction measures should be applied when performing multiple statistical tests to control the increased risk of false positives. However, given the exploratory nature of this study, we did not apply multiple testing correction. We acknowledged this as a limitation of the study and are aware that it may affect the interpretation of the results.

Conclusions

Our study aims to evaluate the causal association between different subtypes of LC and related metabolites, as determined by genetic factors, and the risk of developing SZ. This analysis utilizes a two-sample MR approach, which reveals a statistically significant inverse correlation between ILC levels and the occurrence of SZ. These results suggest that higher levels of ILC may be associated with a decreased risk of developing SZ. Consequently, our findings suggest that ILC may have potential implications in the prevention and treatment of SZ, thereby providing a novel avenue for future research exploring the relationship between metabolism and this psychiatric disorder.

Abbreviations

SZ	Schizophrenia
SNP	Single nucleotide polymorphism
GWAS	Genome-wide association studies
MR	Mendelian randomization
LC	Levo-carnitine
ALC	Acetyl-levo-carnitine
PLC	Propionyl-levo-carnitine
ILC	Isovaleryl- levo-carnitine
IV	Instrumental variable
NGF	Nerve growth factor

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Conceptualization, MJ.Z. and ZJ.F.; methodology, ZJ.F.; software, HY.Q.; validation, HY.Q.; formal analysis, HY.Q.; investigation, HY.Q.; resources, HY.Q.; data curation, HY.Q.; writing—original draft preparation, HY.Q., ZC.Z., TX.W., HR.R.; writing—review and editing, HY.Q., ZJ.F.; visualization, HY.Q.; supervision, ZJ.F.; project administration, MJ.Z. and ZJ.F.; All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

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Competing interests
The authors declare no competing interests.

Author details
[1]School of Biomedical Engineering, Southern Medical University, Guangzhou 510515, China. [2]Second Clinical Medical College, Southern Medical University, Guangzhou 510515, China. [3]Department of Radiation Medicine, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health, Southern Medical University, Guangzhou 510515, China. [4]Postdoctoral Innovation Practice Base, Jiangmen Central Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China.

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