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Investigation of the causal relationship between osteocalcin and dementia: A Mendelian randomization study

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ABSTRACT

Objective: Basic medical studies have reported an improved effect of osteocalcin on cognition. We explored the causal link between osteocalcin and dementia via the implementation of Mendelian randomization methodology.

Methods: Genome-wide association studies were employed to identify single nucleotide polymorphisms (SNPs) showing significant correlations with osteocalcin. Subsequently, A two-sample Mendelian randomization analysis was conducted utilizing the inverse-variance-weighted (IVW) technique to assess the causal relationship between osteocalcin and various types of dementia, including Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body dementia (LBD), and vascular dementia (VD). This approach aimed to minimize potential sources of confounding bias and provide more robust results. Multivariable MR (MVMR) analysis was conducted to adjust for potential genetic pleiotropy.

Results: The study employed three SNPs, namely rs71631868, rs9271374, and rs116843408, as genetic tools to evaluate the causal association of osteocalcin with dementia. The IVW analysis indicated that osteocalcin may have a potential protective effect against AD with an odds ratio (OR) of 0.790 (95 % CI: 0.688–0.906; $P < 0.001$). However, no significant relationship was observed between osteocalcin and other types of dementia. Furthermore, the MVMR analysis indicated that the impact of osteocalcin on AD remained consistent even after adjusting for age-related macular degeneration and Type 2 diabetes with an OR of 0.856 (95 % CI: 0.744–0.985; $P = 0.030$).

Conclusions: Our findings provide important insights into the role of osteocalcin in the pathogenesis of AD. Future research is required to clarify the underlying mechanisms and their clinical applications.

1. Introduction

The term "dementia" refers to a specific set of symptoms, such as memory decline, decreased ability to perform calculations, and

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impaired thinking. There are several types of dementia, including Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body dementia (LBD), and vascular dementia (VD), which reflects specific alterations in the brain [1]. Age has a significant impact on the prevalence of all-cause dementia [2]. According to a forecast report, population aging and growth will result in 2.7 times as many dementia cases worldwide in 2050 as there were in 2019, and more than half of them reside in high-income nations [3]. AD stands as the most prevalent cause of dementia, the increasing number of individuals affected by AD is projected to substantially escalate the overall disease burden [4]. However, limited knowledge on the etiology of dementia has hindered the development of effective control strategies.

New research has uncovered that bones have more functions than previously believed. Apart from providing structural support, bones are also recognized as an endocrine organ capable of secreting various hormones. In light of this, the identification of osteocalcin, an osteoblast-derived hormone, and the variety of physiologic functions it regulates have greatly expanded our understanding of bone biology [5]. Osteocalcin's physiological functions encompass a wide range, including the regulation of glucose metabolism, testosterone synthesis, muscle mass, parasympathetic tone, and brain development and functions [6]. Also of note, some researchers have proposed a new concept: the bone-brain axis [7]. There is a growing body of research to support this view. Animal experimental studies have demonstrated a crucial role of osteocalcin in hippocampal-dependent memory [8]. Lower levels of osteocalcin have been correlated with brain microstructural changes, as well as worse test scores of executive functioning and global cognition in cross-sectional studies of humans [9,10]. However, current epidemiological studies are observational in nature, making it challenging to draw conclusions about the causality between osteocalcin and dementia using conventional statistical methods. On the other hand, although previous observational studies tried to control for every confounding variable to increase their credibility, it is nearly impossible to do so. As a result, unadjusted confounding factors may affect the data showing a correlation between osteocalcin and dementia.

As a new statistical method, the Mendelian randomization (MR) study introduces the idea of an instrumental variable (IV) to address the issues of confounding and reverse causation in traditional epidemiology [11]. An IV is quantifiable and is related to the exposure of interest but unrelated to any other competing risk factor that could potentially confound the results. Genetic variants, as IV in MR study, are used to divide individuals in a population into subgroups. Recent large-scale genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that display significant correlation with osteocalcin [12]. Based on the significant association between osteocalcin and dementia, we conducted a MR study to infer a potential causal relationship between the two. Our hypothesis was that higher concentrations of osteocalcin could potentially decrease the incidence rate of dementia due to the known biological effects of osteocalcin on cognition. To explore this relationship further, we employed a two-sample MR analysis, utilizing summary data from a comprehensive GWAS database. We aimed to obtain robust evidence on the causal association between osteocalcin and dementia.

2. Methods

2.1. Study design

The schematic of the two-sample MR study design is shown in Fig. 1. There are three principal assumptions of MR study for the validity of IV: (1) the selected SNPs should be closely related to osteocalcin; (2) the SNPs must be independent of any confounding

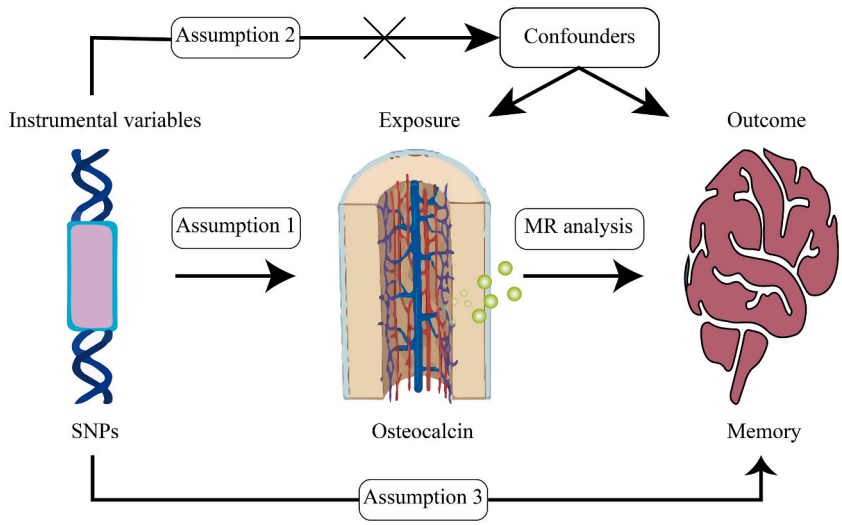

Fig. 1. The two-sample MR study design. Assumption 1: the SNPs should be closely related to osteocalcin; Assumption 2: the SNPs should be independent of confounders of the osteocalcin-dementia associations; Assumption 3: the SNPs can only affect dementia through osteocalcin. Abbreviations: SNPs, Single nucleotide polymorphisms; MR, mendelian randomization.

factors that could impact the association between osteocalcin and dementia; and (3) the SNPs should solely affect dementia through osteocalcin.

2.2. Data source

We obtained the SNPs with osteocalcin from a published GWAS database (ID: prot-a-246) comprising 3301 individuals of European descent. Within this study, 1927 significant associations were identified, involving 1478 proteins and 764 genomic regions [12]. The authors identified genetic factors that play a crucial role in controlling inter-individual variability in the levels of plasma proteins, including osteocalcin.

We subdivided dementia into AD, PD, LBD, and VD in our study. SNPs associated with AD were obtained from the GWAS dataset with ID: ieu-b-2, comprising 21,982 AD patients and 41,944 normal controls [13]; SNPs associated with PD were obtained from the GWAS dataset with ID: finn-b-PD_DEMENTIA_EXMORE, which included 267 PD cases and 111,621 controls [14]; SNPs associated with LBD were obtained from the GWAS dataset with ID: ebi-a-GCST90001390, comprising 2591 LBD cases and 4027 control cases [15]; SNPs associated with VD were obtained from the GWAS dataset with ID: finn-b-I9_VASCDEM, which included 859 VD cases and 211, 300 control cases. All these GWAS were conducted on individuals of European descent and included both male and female participants. Detailed descriptions of the participant data can be found in the original publications and the OpenGWAS website (https://www.gwas.mrcieu.ac.uk).

2.3. SNP selection

Due to the limited number of SNPs available from the open GWAS that had a P value of less than 5.0E-08, we had to rely on genome-wide significant SNPs ($P < 5.0E{-}07$) for our analysis. To ensure that our results were reliable, we conducted a standard clumping procedure to identify independent SNPs. This clumping procedure used a window of 10,000 kb and an LD r^2 cutoff of 0.001. We did not search for proxy SNPs. To validate the first MR assumption, we calculated the proportion of variance in the exposures explained by the SNPs (R^2) and F-statistics of the SNPs. The R^2 values were computed as the sum of 2 X $\beta^2_{exposure}$ X minor allele frequency (MAF) X (1-MAF) for each instrumental SNP. Additionally, we calculated $F = \beta^2_{exposure}/SE^2_{exposure}$ [16,17]. To identify potential confounding factors violating the basic assumptions, we also performed a phenome-wide association study of the SNPs as IV using the online tool (http://www.phenoscanner.medschl.cam.ac.uk) with a P value threshold of 1×10^{-5} [18]. If there were potential confounders on osteocalcin, a multivariable MR (MVMR) analysis was employed to account for potential genetic pleiotropy.

2.4. MR analysis

The MR analysis was conducted using R (version 4.1.2) and involved the TwoSampleMR (Version 0.5.6) and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MRPRESSO) packages (Version 1.0) [19,20]. To ensure the accuracy of the analysis, palindromic SNPs, which represented the same allele in both exposure and outcome data, were removed during the harmonization process. Multiple MR methods were employed to determine the potential causal relationships of osteocalcin with AD, PD, LBD, and VD. The inverse-variance-weighted (IVW) method was employed as the primary analysis method for MR. In cases where no significant heterogeneity was detected ($P > 0.1$ in Cochran's Q analysis), the fixed-effect IVW method was utilized in combination with the standard IVW method. Otherwise, the random-effect IVW method was employed. To generate reliable estimates, two other methods were used based on specific criteria. The weighted-median method was employed when the percentage of invalid IV was $\leq$50 %, while the MR-Egger regression method was applied when the percentage of invalid IVs was 100 %. The MR-Egger method also helped detect and correct potential pleiotropy, as indicated by a significant P value for the intercept (<0.05), to ensure reliable estimates. Moreover, the MRPRESSO's outlier test was used to identify potential outliers, which were subsequently excluded for analysis. Additionally, any horizontal pleiotropy was corrected to provide adjusted results. Leave-one-out analysis was performed to ascertain the impact of individual variants on the outcomes.

2.5. Statistical Analysis

The odds ratios (OR) and their corresponding 95 % confidence intervals (95%CI) were presented for each outcome risk, showing the effect of a 1-standard deviation increase on osteocalcin. The statistical power was determined using a specialized online power calculator (https://shiny.cnsgenomics.com/mRnd/) designed for MR analysis [21]. All reported P values were two-sided. To account for multiple comparisons, we applied the Bonferroni correction (1 exposure and 4 outcomes). As a result, statistical significance was defined as $P < 0.0125$. Any results with P values below 0.05 but above 0.0125 were considered nominally significant.

3. Results

3.1. SNP selection

During the harmonization process of the SNPs and outcome datasets, we removed rs2526393 and rs62143194 because they were palindromic. As a result, we used three remaining SNPs (rs71631868, rs9271374, rs116843408) as genetic instruments to estimate the potential causal relationship between osteocalcin and dementia. (Supplementary Table 1). R^2 value showed that the selected SNPs

could explain 3 % of the variance in the exposure.

3.2. MR Analysis

The fixed effect IVW method was eemployed because there was no significant heterogeneity between the SNPs ($P > 0.1$). The results revealed that genetically determined osteocalcin levels were significantly related to a lower risk of AD (OR = 0.790; 95 % CI: 0.688–0.906; $P < 0.001$; Fig. 2A). These findings were inline with the weighted median method (OR = 0.761; 95 % CI: 0.644–0.900; P = 0.001), but not with the MR-Egger regression method (OR = 1.387; 95 % CI: 0.527–3.562; P = 0.628). On the other hand, genetically determined osteocalcin levels were not related to PD (Fig. 2B), LBD (Fig. 2C), and VD (Fig. 2D). The results were consistent across all three analysis methods. The scatter plots depicting the associations between genetically predicted osteocalcin levels and dementia are shown in Supplementary Fig. 1.

The MR-Egger intercept test demonstrated no significant evidence of pleiotropic bias. The MRPRESSO test analysis did not detect

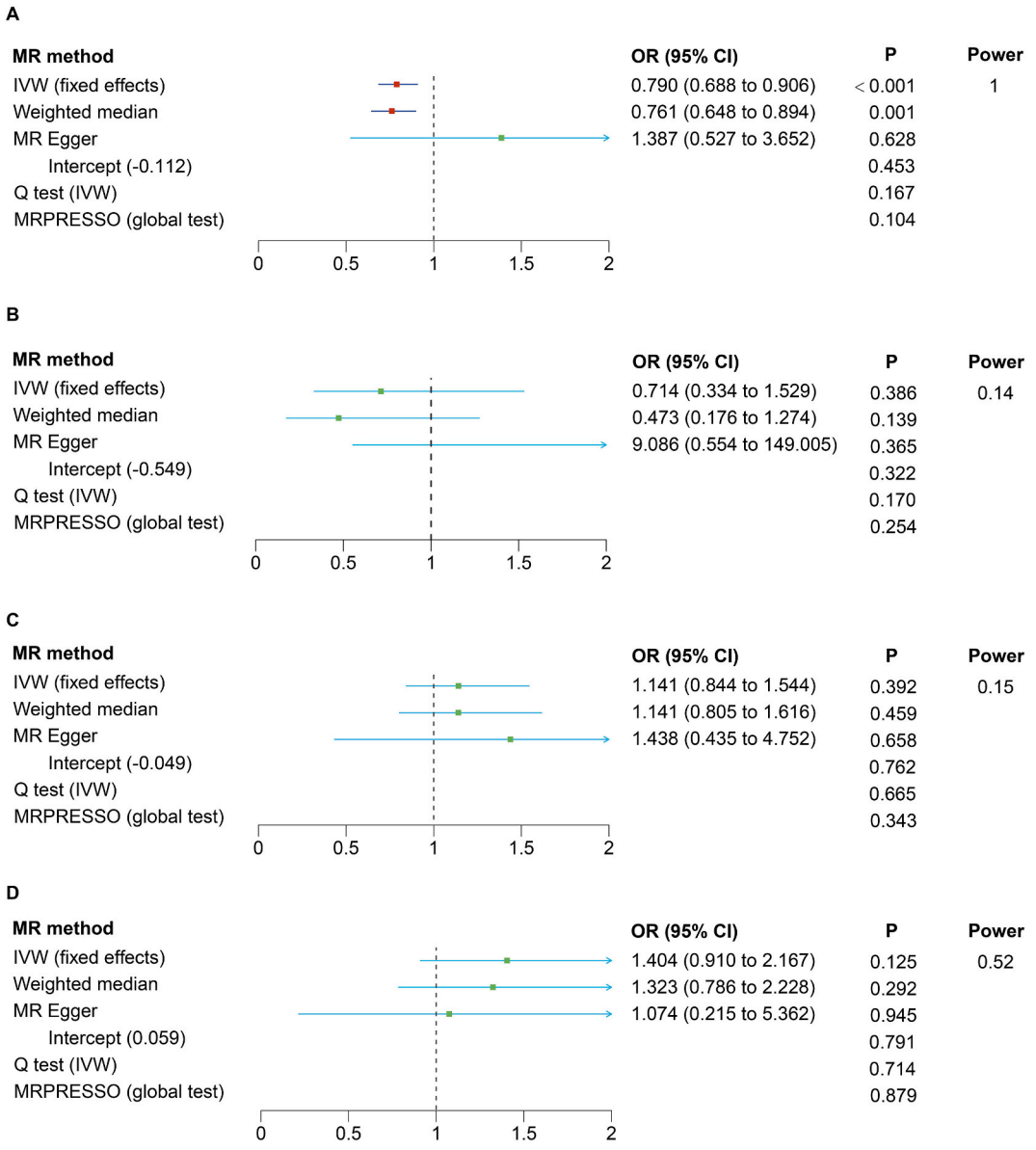

Fig. 2. Forest plot displaying causal effect estimates of osteocalcin on dementia. A: AD and osteocalcin. B: PD and osteocalcin. C: LBD and osteocalcin. D: VD and osteocalcin. Abbreviations: MR, mendelian randomization; IVW, inverse-variance–weighted; MRPRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, odds ratios; CI, confidence intervals; AD, Alzheimer's disease; PD, Parkinson's disease; LBD: Lewy body dementia; VD: vascular dementia.

any outliers in the estimates. Furthermore, the leave-one-out analysis revealed that the risk estimates for dementia and genetically predicted osteocalcin levels remained unchanged even after excluding one SNP at a time. These results indicated no single SNP with potentially significant influence on the causal association (Supplementary Fig. 2).

3.3. MVMR Analysis

After conducting a PhenoScanner search, we identified rs71631868 and rs9271374 are related to age-related macular degeneration and Type 2 diabetes. To account for these associations, we utilized MVMR analysis to adjust osteocalcin levels. Genetic variants of age-related macular degeneration and Type 2 diabetes were obtained from a GWAS (ID: finn-b-H7_AMD) and a GWAS (ID: ebi-a-GCST008048), respectively. Table 1 shows that the impact of osteocalcin on AD remained largely unchanged even after accounting for age-related macular degeneration and Type 2 diabetes (OR = 0.856; 95 % CI: 0.744–0.984; P = 0.030). This suggests the result is robust and stable.

4. Discussion

In this study, we executed Mendelian randomization (MR) and multivariable Mendelian randomization (MVMR) analyses to assess the relationship between genetically determined osteocalcin and dementia. Our primary finding from MR showed a significant correlation a significant relationship between the decline in AD and genetic susceptibility to osteocalcin, and this finding was supported by MVMR analyses with adjustments for age-related macular degeneration and Type 2 diabetes. Nevertheless, our research did not identify any significant correlation between osteocalcin and PD, LBD, or VD. Notably, our study may be the first to investigate the causal associations between osteocalcin and dementia utilizing large-scale GWAS data. According to the idea of MR, any association of the genetic variant with AD must come via the variant's association with osteocalcin, and therefore implies a causal effect of osteocalcin on AD.

The pathogenic mechanism underlying AD remain a subject of ongoing debate. Several risk factors, such as genetics [22] and insufficient physical activity [23], have been suggested to potentially contribute to the development of AD. Currently, there is no definitive cure for AD, and treatments aiming to slow progression have shown only limited success [24]. As a result, most interventions seek to reduce AD's symptoms. Recognizing the intricate link between bone and brain, our research focused on the potential involvement of bone-secreted proteins in AD and explored the possibility of developing innovative therapeutic approaches by targeting bone-brain interactions. Specifically, we investigated osteocalcin, a non-collagenous protein exclusively secreted by osteoblasts and commonly used as a biomarker for bone formation. Recent research has brought attention to osteocalcin as a hormone with a range of physiological functions, including the regulation of brain growth and function [25].

The relationship between osteocalcin and AD remains unclear due to conflicting evidence. One case-control study revealed lower serum osteocalcin levels in individuals with AD in comparison with the same-aged normal population, implying potential poor bone health [26]. However, a different cross-sectional study reported a negative correlation between serum osteocalcin levels and the Montreal Cognitive Assessment score, revealing that early-stage AD patients had significantly higher levels of serum osteocalcin than normal population [27]. Moreover, preclinical medical experiments have shown evidence suggesting that the Swedish mutant amyloid precursor protein (APP) might suppress osteoblastogenesis and osteocalcin secretion [28]. Some herbal drugs have been reported to show positive effects on AD and bone loss [29]. However, the available data on the associations between osteocalcin and AD are vulnerable to various potential biases, such as residual confounding and reverse causality. As the knowledge of the human genome has developed, it is now possible to improve causal inference in exposure-disease associations using MR design that uses genetic variants as exposure. Therefore, we employed this method to overcome the problems of confounding and reverse causation in conventional epidemiology. Our results revealed an association between higher osteocalcin level and reduced risk of AD, suggesting that osteocalcin could be a novel therapeutic target in the future.

The described relationship between osteocalcin and AD was also assessed with respect to their biological plausibility. According to previous studies, several G-protein-coupled receptors (GPR) mediate the beneficial effect of osteocalcin on cognition. By binding to GRP158 in pyramidal neurons of the CA3 region of the hippocampus, osteocalcin promotes the accumulation of inositol 1,4,5-trisphosphate and brain-derived neurotrophic factor in neurons, leading to improved long-term potentiation and amelioration of age-related memory loss [8,30]. Recently, osteocalcin has been reported to mediate the transition between oligodendrocyte precursor cells and myelinating oligodendrocyte via GPR37 signaling [31]. Research has linked myelin breakdown in oligodendrocytes to an increased risk of AD. This breakdown may represent the early changes in the disease, preceding the development of amyloid and tau pathology [32]. However, it's worth noting that osteocalcin also plays a vital role in acute stress responses. Levels of osteocalcin increase rapidly in response to stressors in both rodents and humans [33]. Therefore, a representative measurement for an individual is difficult to define, as this cellular phenotype changes over time. The causal influence of osteocalcin on the risk of developing AD can, however, be

Table 1
Results of MVMR adjusting for the effect of age-related macular degeneration and Type 2 diabetes.

Exposure	Outcome	Beta	SE	OR (95 % CI)	P
Type 2 diabetes	AD	0.007	0.035	1.007 (0.939–1.080)	0.843
Age-related macular degeneration	AD	−0.096	0.052	0.908 (0.820–1.006)	0.065
Osteocalcin	AD	−0.155	0.072	0.856 (0.744–0.985)	0.030

evaluated by MR because the genetic variant can be measured. The SNPs rs71631868 and rs9271374 are associated with age-related macular degeneration. Our MVMR results align with previous MR analyses showing no evidence supporting a bidirectional causal relationship between age-related macular degeneration and AD [34]. However, our findings show some inconsistencies with a systematic review reporting higher risks of dementia or AD among patients with age-related macular degeneration [35]. It's worth noting that the SNP rs9271374, which was used in our MVMR analysis, is also associated with Type 2 diabetes. AD has been considered type 3 diabetes [36], and a prior study has identified a causal relationship between diabetes and an increased risk of AD [37]. As AD, age-related macular degeneration, and Type 2 diabetes are complex and chronic diseases, a comprehensive understanding of the shared pathophysiological mechanisms between them is required.

Different MR results among AD and PD, VD, LPD are attributed to their different etiologies. Earlier research has demonstrated that in animal models, osteocalcin has a protective effect against neurodegeneration associated with PD, particularly in the improvement of motor impairments [38,39]. However, we were unable to establish a causal association between osteocalcin and dementia due to PD. There are few reports concerned with the relationship between osteocalcin and LPD or VD. Additional research is required validate whether the observed result is a true negative.

Our study had several limitations. First, to minimize potential biases resulting from population stratification, the study population was limited to individuals of findings to other racial or ethnic groups. Second, in our effort to identify more SNPs associated with osteocalcin, we set the P value of genome-wide significance at 5.0E-07. Fortunately, the selected SNPs demonstrated F statistics higher than 10, which helped mitigate the effect of weak instrument bias. Third, we recognize that our study may have had limited statistical power to explore the relationship between osteocalcin and certain conditions, such as PD, LBD, and VD. Therefore, larger clinical prospective studies are necessary to further investigate these associations in greater depth.

5. Conclusions

In summary, this MR study established that osteocalcin is involved in AD and, in contrast, was not involved in dementia to PD, LBD, or VD. A higher circulating level of osteocalcin may act as a neuroprotectant against AD. Modifications to osteocalcin may be worth exploring in future efforts to prevent this devastating disease.

Author contribution statement

Wangmi Liu, Qiang Hu: Performed the experiments; Wrote the paper.Feng Zhang: Analyzed and interpreted the data. Kesi Shi: Contributed reagents, materials, analysis tools or data. Jiayan Wu: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21073.

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