The Magnesium Connection: Impact on Erectile Dysfunction and Mortality

Xiaobao Chen
Fujian Medical University Union Hospital
Ruoyun Xie
Fujian Medical University Union Hospital
Binhong Liu
Fujian Medical University Union Hospital
Junwei Lin
Fujian Medical University Union Hospital
Wei Jiang
Fujian Medical University Union Hospital
Huaiying Zheng
uro2159@126.com

Fujian Medical University Union Hospital

Article

Keywords: erectile dysfunction, sexual dysfunction, magnesium deficiency, Mortality, NHANES

Posted Date: October 15th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4888062/v1

Additional Declarations: No competing interests reported.

Abstract

This research examines both the cross-sectional and longitudinal relationships between magnesium depletion score (MDS) and erectile dysfunction (ED), as well as all-cause mortality in individuals diagnosed with ED. The analysis utilized data from the National Health and Nutrition Examination Survey (NHANES). To evaluate the correlation between MDS and ED, along with mortality outcomes, weighted multivariate regression and Cox proportional hazards models were employed. Out of the total 3,917 participants, 1,090 were identified as having ED, and 654 individuals succumbed to all-cause mortality. After controlling for potential confounding variables, it was found that each incremental increase of one point in MDS correlated with a 37% heightened risk of developing ED (OR: 1.37, 95% CI: 1.16–1.62). Furthermore, among those with ED, a greater MDS score was linked to a 30% elevation in the risk of all-cause mortality (HR: 1.30, 95% CI: 1.17–1.45). Sensitivity analyses, which included subgroup evaluations and propensity score matching (PSM), validated the robustness of these results. The findings indicate a significant association between MDS and both the prevalence of ED and the risk of all-cause mortality in individuals suffering from ED, highlighting the critical role of magnesium status in the health of men.

Introduction

Erectile dysfunction is a prevalent condition among men, particularly those over the age of 40, and it has significant implications for quality of life and overall health[1]. ED is characterized by the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. The etiology of ED is multifactorial[2–9], with vascular, neurogenic, hormonal, and psychological factors all playing roles. In recent years, there has been increasing interest in the role of micronutrients, including magnesium, in the pathophysiology of ED[10].

Magnesium is an essential mineral involved in numerous physiological processes, including the metabolism of nitric oxide, a critical mediator of penile erection[11]. Hypomagnesemia, or magnesium deficiency, has been implicated in various cardiovascular and metabolic disorders, which are also risk factors for ED. Despite the biological plausibility linking magnesium status to erectile function, the relationship between magnesium deficiency and ED has not been extensively studied.

Previous research has shown that hypomagnesemia is associated with an increased prevalence of ED in certain populations. For instance, a study on elderly men with chronic kidney disease found that those with hypomagnesemia had a significantly higher prevalence of ED compared to those with normal magnesium levels[10]. Additionally, dietary intake of magnesium and other trace metals has been inversely associated with the prevalence of ED, suggesting that adequate intake of these nutrients may be protective against the development of ED[12]. The concept of a Magnesium Depletion Score (MDS) has been proposed as a composite measure to assess magnesium status in individuals. Conventional methods rely on serum magnesium levels, which may not accurately reflect total body magnesium content, as serum levels constitute only 0.3% of total body magnesium[13]. This discrepancy can lead to underdiagnosis of chronic magnesium deficiency, even when serum levels appear normal. The Magnesium Tolerance Test (MTT) is recognized as a reliable method for assessing magnesium status, but its complexity and procedural requirements limit its clinical use[14,15]. In response, Fan et al.[16] developed the MDS, offering a more accessible and accurate tool for identifying magnesium deficiency. The MDS considers factors such as diuretic and proton pump inhibitor usage, changes in renal function, and alcohol consumption, providing a comprehensive assessment that surpasses the limitations of serum and urinary magnesium measures. Understanding the relationship between MDS and ED could provide insights into potential preventive and therapeutic strategies for ED.

Furthermore, magnesium deficiency has been linked to increased all-cause mortality, highlighting the broader health implications of maintaining adequate magnesium levels[17]. Given the potential impact of magnesium on both erectile

function and overall mortality, it is important to investigate these relationships comprehensively.

This study aims to explore the association between ED and MDS, utilizing data from the NHANES conducted between 2001 and 2004. Additionally, we will analyze the relationship between MDS and all-cause mortality, providing a holistic view of the health implications of magnesium deficiency. By leveraging a large, nationally representative dataset, this research seeks to contribute to the understanding of the role of magnesium in erectile function and overall health.

Materials and methods

Study population

This investigation employed data sourced from the NHANES conducted during the period from 2001 to 2004. The cohort consisted of individuals who had complete datasets pertaining to ED and MDS. Trained interviewers conducted extensive family interviews to collect relevant information, encompassing demographic characteristics, educational attainment, and personal medical histories. Individuals lacking complete demographic data, clinical outcomes, or laboratory results were excluded from the analysis. Ethical approval was secured, along with informed consent from the National Center for Health Statistics Research Ethics Review Board, which was duly communicated to all participants involved. Rigorous procedures were established for data collection and definition.

Assessment of ED

During the NHANES data collection period, interviews with participants were conducted in private rooms within the Mobile Examination Center (MEC). ED was assessed using the Audio Computer-Assisted Self-Interview (ACASI) method. Participants were asked to describe their ability to achieve and maintain satisfactory erectile function, with response options ranging from 'always or almost always able to,' 'usually able to,' 'sometimes able to,' to 'unable to' Participants who reported being 'sometimes able to' or 'unable to' in maintaining an erection were classified as having erectile dysfunction, while those who reported 'always or almost always able to' or 'usually able to' were considered not to have erectile dysfunction. This assessment question was adapted from the Massachusetts Male Aging Study[18].

All individuals who fulfilled the eligibility requirements and possessed adequate identifying information were connected with mortality records. This linkage was performed by the research data center at the National Center for Health Statistics, employing the National Death Index. The connection was established using the Linked Mortality Files, which are accessible to the public through the National Center for Health Statistics. The main emphasis of the outcomes was on fatalities attributed to any cause. The follow-up period commenced upon the completion of the NHANES questionnaire and concluded either at the time of death or on December 31, 2019.

Assessment of MDS

The MDS is calculated using the methodology described elsewhere[16], incorporating four factors: (1) a score of 1 for current diuretic usage, (2) a score of 1 for current proton pump inhibitor usage, (3) a score of 1 for exceeding the recommended alcohol consumption limits, and (4) a score of 1 for mild decline in renal function and a score of 2 for chronic kidney disease. The estimated glomerular filtration rate (eGFR) of participants was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. 1[9]. The renal function was categorized into three groups: normal renal function (eGFR $\geq$ 90 mL/(min 1.73 m²)), mild renal impairment (60 mL/(min 1.73 m²) $\leq$ eGFR < 90 mL/(min 1.73 m²)), and chronic kidney disease (eGFR < 60 mL/(min 1.73 m²)).

Covariates

The collection of variables in this study includes demographic characteristics such as age, BMI, marital status, education level, race, and family income. Lifestyle habits like physical activity and smoking status are also considered,

along with dietary consumption including dietary magnesium intake and total energy intake. Additionally, comorbid conditions such as coronary heart disease, hypertension, metabolic syndrome, anemia, and hypertension are taken into account, as well as laboratory biochemical indicators.

Diabetes was diagnosed based on a glycosylated hemoglobin (HbA1c) level ≥ 6.5%, fasting blood glucose level ≥ 126 mg/dL, use of antidiabetic medications, or self-report. Diagnosis of hypertension was based on systolic/diastolic blood pressure values ≥ 140/90 mmHg, use of antihypertensive medications, or self-report. Diagnoses of coronary artery disease included heart failure, coronary artery disease, angina, or myocardial infarction. Anemia is determined by hemoglobin levels, with two groups: no anemia (≥ 130 g/L) and anemia (< 130 g/L).

The identification of metabolic syndrome in adult populations is based on the criteria established by the National Cholesterol Education Program's Adult Treatment Panel III[20,21]. This framework stipulates that the diagnosis requires the presence of a minimum of three risk factors, which include: 1) waist circumference ≥ 102 cm for men and ≥ 88 cm for women; 2) Serum triglycerides ≥ 150 mg/dL; 3) HDL cholesterol < 40 mg/dL for males and < 50 mg/dL for females; 4) Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; 5) Fasting blood glucose ≥ 100mg/dL.

Information regarding dietary magnesium consumption (mg/day) and overall energy intake was gathered through two separate 24-hour dietary recall interviews. These interviews documented the participants' comprehensive energy and nutrient consumption from all food items and beverages. The first phase of data collection took place at the Mobile Examination Center (MEC), while a subsequent interview was carried out via telephone between 3 to 10 days later. To ensure the objectivity of the results, we computed the mean magnesium intake alongside the total energy intake for each participant, utilizing the data obtained from both interview sessions.

Statistical analysis

In the course of our data analysis, we adhered to the analytical protocols established by the NHANES. Importantly, none of the variables examined in our study exhibited missing data that surpassed the threshold of 10%. To accommodate the intricate sampling design inherent to NHANES, all statistical analyses were conducted utilizing the designated sample weights. We calculated weighted means along with standard errors for continuous variables, and comparisons were performed employing either Student's t-test or one-way analysis of variance. For categorical data, we presented the results as weighted percentages accompanied by standard errors, and intergroup comparisons were executed using chi-square tests.

A comprehensive weighted multivariable logistic regression analysis was performed to explore the association between MDS and ED. The analysis included adjustments for sociodemographic characteristics, lifestyle behaviors, dietary factors, comorbidities, and laboratory data. In addition, a multivariable weighted Cox proportional hazards regression analysis was utilized to investigate the relationship between MDS and all-cause mortality. Moreover, weighted Kaplan-Meier curves and log-rank tests were used to analyze cumulative survival differences across different MDS categories.

To ensure the robustness of our study results, we conducted several sensitivity tests. Initially, MDS was categorized as a categorical variable, with MDS = 0 as the reference category, to assess distinct patterns in the relationships. Subsequently, the population was stratified based on factors such as diabetes, cardiovascular diseases, hypertension, anemia, cancer, metabolic syndrome, and magnesium intake for subgroup analysis. Interaction tests were utilized to evaluate heterogeneity among different subgroups. Furthermore, different definitions of ED were employed for analysis, distinguishing participants who were unable or sometimes able to achieve and maintain satisfactory erections for sexual intercourse as having mild or severe erectile dysfunction. Lastly, the MDS was split into two groups: MDS = 0 and MDS > 0. Propensity score matching analysis was then conducted to further investigate the relationship between MDS and ED, as well as the survival outcomes in patients with ED.

All analyses were performed using the statistical software packages R (R version 4.2.0) and Free Statistics software version 1.9.

Results

Participant characteristics

The demographic characteristics of participants are presented in Table 1. Following screening, 3,917 cases fulfilled the criteria (Figure 1). The MDS for the ED group was 1.32±0.05, with a magnesium intake of 291.74±7.17 mg. In contrast, the non-ED group exhibited an MDS of 0.72±0.03, with an intake of 336.22±4.32 mg. The proportion of older adults and cohabitants is higher in the ED group compared to the non-ED group. Furthermore, the ED group exhibits higher proportions of elevated BMI, smoking rate, diabetes, cardiovascular disease, hypertension, cancer, anemia, and MetS. Additionally, the MDS in the ED group is significantly higher than that in the non-ED group(Figure 2A). Within each subgroup of MDS, the prevalence of ED increased significantly with higher MDS (Figure 2B).

The association between MDS and ED

Table 2 displays the outcomes of the weighted logistic regression analysis examining the relationship between MDS and ED. The findings reveal a positive association between MDS and ED across various adjusted models. In the unadjusted model, the ORs were 2.11 (95% CI: 1.88-2.35, $p < 0.001$). Following adjustment for all covariates, the ORs decreased to 1.41 (95% CI: 1.20-1.67, $p < 0.001$).

To further analyze the data, we stratified the MDS into comparative groups, establishing the MDS=0 category as the reference point. In the unadjusted model, the OR demonstrated a significant increase, ranging from 2.03 (95% CI: 1.58-2.61) to a notably higher value of 12.99 (95% CI: 8.47-19.91). Upon adjustment, the increment in OR was attenuated; however, it still exhibited a substantial rise from 1.50 (95% CI: 0.84-2.66) to 3.01 (95% CI: 1.1-8.21). This pattern of correlation remained consistent across various adjusted models, confirming a linear trend that achieved statistical significance (p for trend < 0.05).

Subgroup analysis

Table 3 delineates the intricate results of subgroup analyses and interaction tests, which explore the influence of stratification on the correlation between MDS and ED. The data consistently reveal a positive association between MDS and ED across all examined subgroups, with this relationship persisting even after meticulous adjustments for potential confounding covariates. In the realm of interaction effects, a noteworthy interaction was identified solely in the context of cancer history, with statistical significance indicated by a p-value less than 0.05. Conversely, no such interactions were observed for the remaining variables. The subgroup analysis, particularly among participants without a history of cancer, demonstrates that those with an MDS of ≥3 are at a significantly elevated risk of ED, with a 2.68-fold increase compared to those with an MDS of 0 (95% CI: 1.83-7.41). Furthermore, a compelling linear relationship between the MDS and the risk of ED is evident, underscored by a highly significant p-value for the trend test ($p < 0.001$). Regarding trend tests, the linear association was found to be non-significant for anemia, cancer, and high levels of magnesium intake, as indicated by a p-value exceeding 0.05. However, for all other variables, a pronounced linear relationship is discernible.

Sensitivity analysis

To further minimize the impact of confounding variables, we utilized PSM analysis to categorize MDS into MDS=0 and MDS>0 groups. The findings (Supplement Table 2) consistently reveal a significant association between MDS and ED across different propensity score techniques. Specifically, using the IPTW method, the likelihood of developing ED was found to be 67% higher in the MDS>0 group compared to the MDS=0 group (OR 1.67, 95% CI 1.41-1.97).

The association of mortality with different MDS and ED status.

Over a median follow-up period of 206 months, our study meticulously identified 1,116 cases of all-cause mortality within the entire cohort, with a notable 654 cases occurring in the ED group. The baseline characteristics of the ED participants, categorized by overall survival (OS), are succinctly detailed in Supplement Table 1.A rigorous multifactorial Cox regression analysis revealed significant prognostic disparities associated with various combinations of MDS and ED status. Specifically, the prognosis for the MDS>0 and ED group was markedly poorer compared to the MDS=0 and non-ED group, with a HR of 2.18(95% CI: 1.61- 2.96)(Table 4). The Kaplan-Meier curves, delineated in Figure 3, vividly portray the survival rates for all-cause mortality across these distinct MDS and ED groupings. Further assessment of the influence of MDS on prognosis within the ED group, outlined in Table 5, underscored a direct correlation that higher MDS were linked to a more adverse prognosis. After accounting for various confounding factors, individuals with MDS of 1, 2, and ≥3 were observed to have a 98%, 161%, and 179% increased risk of all-cause mortality, respectively, compared to those with an MDS of 0 (HR 1.98, 95% CI 1.22-3.21; HR 2.61, 95% CI 1.58-4.3; HR 2.79, 95% CI 1.73-4.49).The Kaplan-Meier curves, elegantly depicted in Figure 4, illustrate the stark survival differences based on MDS. Notably, participants with MDS of ≥3 exhibited the lowest survival rate, while those with scores of 1 or 2 demonstrated an intermediate rate. In contrast, participants with an MDS of 0 enjoyed the highest survival rate, with the survival disparities being statistically significant as indicated by the log-rank test (P<0.001).

To address potential confounding factors, PSM was conducted as a sensitivity analysis (Supplement Table 3). The consistent findings across various PSM methods demonstrated that individuals with MDS >0 had a 0.67-1.4 times higher risk of all-cause mortality compared to those with MDS of 0.

Discussion

This investigation sought to explore the correlation between MDS and ED, and further analyze the association between MDS and all-cause mortality. Our results indicated a significant relationship, wherein elevated MDS was correlated with an increased likelihood of experiencing ED. This aligns with our hypothesis that magnesium deficiency, as indicated by MDS, could be a contributing factor to ED. Additionally, our analysis revealed a significant association between higher MDS and increased all-cause mortality, suggesting that magnesium deficiency could have broader health implications beyond ED. These results highlight the necessity of considering magnesium levels in the therapeutic approach to ED and emphasize the potential public health significance of addressing magnesium deficiency.

Our study provides a novel insight into the relationship between ED and the MDS, filling a significant gap in the existing literature. Previous studies[22,23] have primarily focused on the role of individual micronutrients in ED or the broader implications of magnesium deficiency on cardiovascular and metabolic health. However, the comprehensive assessment of MDS, which includes factors like diuretic use, proton pump inhibitor use, excessive alcohol consumption, and renal function decline, offers a more holistic view of how magnesium status affects ED. The weighted multivariable logistic regression analysis demonstrating a positive correlation between MDS and ED, even after adjusting for confounding variables, underscores the potential pathophysiological link between magnesium deficiency and erectile function. This study also explores the impact of MDS on all-cause mortality within the ED population, revealing that higher MDS is associated with significantly increased mortality risk. This dual focus on ED and mortality provides a more in-depth understanding of the broader health implications of magnesium deficiency. Compared to previous research, our findings are the first to systematically quantify the risk of ED and mortality based on a composite score of magnesium deficiency, thus offering new avenues for clinical assessment and intervention strategies[24].

The findings of this study have significant clinical implications, particularly in the management and prevention of ED and the associated risks of all-cause mortality. The observed positive correlation between MDS and ED highlights the

potential role of magnesium in maintaining vascular health and erectile function. Given that magnesium is involved in numerous physiological processes, including vasodilation and endothelial function, its deficiency could exacerbate vascular conditions that contribute to ED. Clinicians should consider assessing magnesium levels in patients presenting with ED, especially those with other risk factors such as diabetes, hypertension, and cardiovascular diseases. Furthermore, our study suggest that addressing magnesium deficiency through dietary modifications or supplementation could be a viable strategy to mitigate ED and potentially improve overall prognosis. This is particularly relevant for older adults and individuals with chronic health conditions who are at higher risk of both magnesium deficiency and ED. Additionally, the strong association between higher MDS and increased all-cause mortality underscores the importance of comprehensive nutritional assessments in clinical practice. By identifying and correcting magnesium deficiency, healthcare providers may not only improve erectile function but also enhance long-term survival outcomes. Future research should focus on interventional studies to confirm these findings and explore the efficacy of magnesium supplementation as a therapeutic approach for ED.

Magnesium deficiency is prevalent in cancer patients[24–29], potentially caused by decreased magnesium intake and absorption, along with elevated excretion due to tumor-related medications. The subgroup analysis findings of this study indicate a more pronounced link between MDS and cancer in individuals with a prior history of cancer. Hence, addressing magnesium deficiency in the cancer population should be a priority.

This study presents several strengths. Firstly, it benefits from a large and representative sample of the US population, encompassing two cycles of cross-sectional data. This ample sample size ensures sufficient statistical power for rigorous analysis. Secondly, the application of sampling weights enhances the generalizability and representativeness of the survey findings at a national level. Thirdly, the researchers meticulously accounted for various potential confounding factors, drawing on prior research and clinical expertise to bolster the reliability and validity of the results. Fourthly, the study opted for MDS over serum magnesium, as the former offers a more accurate reflection of magnesium's physiological status. Lastly, sensitivity analyses were performed to confirm the robustness and reliability of the findings. Nonetheless, it is crucial to recognize certain limitations inherent in this study. Firstly, the reliance on NHANES cross-sectional data hinders the ability to establish causal relationships between MDS and ED. Secondly, despite attempts to control for potential confounders, the impact of unmeasured or residual confounders cannot be entirely eradicated. Moreover, the absence of serum magnesium data in the NHANES database prevented a comparison between MDS and serum magnesium levels. Lastly, caution should be exercised when extrapolating the study results to other populations, as they may be specific to the US population. Future research should aim to address these limitations by conducting longitudinal studies to establish temporal relationships and causal inferences. Additionally, randomized controlled trials (RCTs) investigating the effects of magnesium supplementation on ED and overall mortality are warranted. Such studies should also explore the underlying biological mechanisms linking magnesium deficiency to ED and mortality. Moreover, the development and validation of more precise and comprehensive tools for assessing magnesium status in clinical settings could enhance the accuracy of future research. By addressing these gaps, future studies can provide more definitive evidence on the role of magnesium in ED and broader health outcomes, potentially informing clinical guidelines and public health strategies for the prevention and management of magnesium deficiency and its associated risks.

Conclusion

In summary, this study highlights a significant association between ED and MDS. Our findings suggest that higher MDS, indicative of magnesium deficiency, is correlated with an increased risk of ED. Additionally, the analysis reveals that elevated MDS is also associated with higher all-cause mortality rates. These results underscore the potential importance of magnesium status in the management and prognosis of ED and overall health outcomes.

Declarations

Competing interests

The authors declare no conflict of interest.

Ethics disclosures

The NHANES was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board(https://www.cdc.gov/nchs/nhanes/ irba98. htm).

Funding

This work was supported by the Startup Fund for Scientific Research,Fujian Medical University[Grant number 2020QH1081]

Author Contribution

Xiaobao Chen: conceptualization, data curation, formal analysis, investigation, methodology, software, visualization, and writing - original draft; Ruoyun Xie: validation and resources; Binhong Liu: investigation and writing - review and editing; Junwei Lin and Wei Jiang: methodology, supervision, visualization, and writing - review and editing; Huaiying Zheng: funding acquisition, project administration, supervision, and writing - review and editing.

Acknowledgments

None.

Data Availability

The datasets used for this study are publicly available from the National Center for Health Statistics website[https:// www. cdc. gov/ nchs/ nhanes/ index. htm].

References

1. Guay, A. T. et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: a couple's problem–2003 update. *Endocr. Pract.* **9**, 77–95 (2003).
2. Wessells, H., Joyce, G. F., Wise, M. & Wilt, T. J. Erectile dysfunction. *J. Urol.* **177**, 1675–1681 (2007).
3. Goldstein, I., Goren, A., Li, V. W., Tang, W. Y. & Hassan, T. A. Epidemiology Update of Erectile Dysfunction in Eight Countries with High Burden. *Sex. Med. Rev.* **8**, 48–58 (2020).
4. Pellegrino, F. et al. Relationship Between Age, Comorbidity, and the Prevalence of Erectile Dysfunction. *Eur. Urol. Focus*. **9**, 162–167 (2023).

5. Hadisuyatmana, S., Malik, G., Efendi, F., Reisenhofer, S. & Boyd, J. The experiences and barriers in addressing type 2 diabetes mellitus-associated erectile dysfunction: a mixed method systematic review. *Syst. Rev.* **12**, 138 (2023).
6. Terentes-Printzios, D., Ioakeimidis, N., Rokkas, K. & Vlachopoulos, C. Interactions between erectile dysfunction, cardiovascular disease and cardiovascular drugs. *Nat. Rev. Cardiol.* **19**, 59–74 (2022).
7. Pizzol, D. et al. Prevalence of erectile dysfunction in patients with chronic kidney disease: a systematic review and meta-analysis. *Int. J. Impot. Res.* **33**, 508–515 (2021).
8. Verze, P., Margreiter, M., Esposito, K., Montorsi, P. & Mulhall, J. The Link Between Cigarette Smoking and Erectile Dysfunction: A Systematic Review. *Eur. Urol. Focus*. **1**, 39–46 (2015).
9. Lai, L. T. F., Balaraman, J., Zhou, F. & Matthies, D. Cryo-EM structures of human magnesium channel MRS2 reveal gating and regulatory mechanisms. *Nat. Commun.* **14**, 7207 (2023).
10. Toprak, O., Sarı, Y., Koç, A., Sarı, E. & Kırık, A. The impact of hypomagnesemia on erectile dysfunction in elderly, non-diabetic, stage 3 and 4 chronic kidney disease patients: a prospective cross-sectional study. *Clin. Interv Aging*. **12**, 437–444 (2017).
11. First, M. R., Henning, A. K. & Fitzsimmons, W. E. Use of low-dose tacrolimus and associated hypomagnesemia in the prevention of erectile dysfunction following prostatectomy for prostate cancer. *Pharmacol. Rep.* **68**, 1154–1158 (2016).
12. Liu, R. J. et al. Dietary metal intake and the prevalence of erectile dysfunction in US men: Results from National Health and Nutrition Examination Survey 2001–2004. *Front. Nutr.* **9**, 974443 (2022).
13. Dominguez, L. J., Veronese, N. & Barbagallo, M. Magnesium and the Hallmarks of Aging. *Nutrients* **16** (2024).
14. Witkowski, M., Hubert, J. & Mazur, A. Methods of assessment of magnesium status in humans: a systematic review. *Magnes Res.* **24**, 163–180 (2011).
15. Simşek, E., Karabay, M. & Kocabay, K. Assessment of magnesium status in newly diagnosed diabetic children: measurement of erythrocyte magnesium level and magnesium tolerance testing. *Turk. J. Pediatr.* **47**, 132–137 (2005).
16. Fan, L. et al. Magnesium Depletion Score (MDS) Predicts Risk of Systemic Inflammation and Cardiovascular Mortality among US Adults. *J. Nutr.* **151**, 2226–2235 (2021).
17. Petrakis, I. et al., *Cardiovascular and All-Cause Mortality Is Affected by Serum Magnesium and Diet Pattern in a Cohort of Dialysis Patients. J. Clin. Med.* 13 (2024).
18. Kessler, A., Sollie, S., Challacombe, B., Briggs, K. & Van Hemelrijck, M. The global prevalence of erectile dysfunction: a review. *BJU Int.* **124**, 587–599 (2019).
19. Levey, A. S. et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **150**, 604–612 (2009).
20. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Jama*. **285**, 2486–2497 (2001).
21. Grundy, S. M., Brewer, H. B. Jr., Cleeman, J. I., Smith, S. C. Jr. & Lenfant, C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 109, 433–438 (2004).
22. Rosique-Esteban, N., Guasch-Ferré, M. & Hernández-Alonso, P. & Salas-Salvadó, J. Dietary Magnesium and Cardiovascular Disease: A Review with Emphasis in Epidemiological Studies. *Nutrients* 10 (2018).
23. De Lorenzo, A. et al. The effects of Italian Mediterranean organic diet (IMOD) on health status. *Curr. Pharm. Des.* **16**, 814–824 (2010).
24. Houston, M. The role of magnesium in hypertension and cardiovascular disease. *J. Clin. Hypertens. (Greenwich)*. **13**, 843–847 (2011).

25. Nguyen, L. T. D. et al., *The interaction between magnesium intake, the genetic variant INSR rs1799817 and colorectal cancer risk in a Korean population: a case-control study. Int. J. Food Sci. Nutr., 1–11* (2024).
26. Liu, W. et al., *Dietary Magnesium Replacement for Prevention of Hypomagnesemia in Patients With Ovarian Cancer Receiving Carboplatin-Based Chemotherapy. JCO Oncol Pract, Op2300660* (2024).
27. Ashique, S. et al. A narrative review on the role of magnesium in immune regulation, inflammation, infectious diseases, and cancer. *J. Health Popul. Nutr.* **42**, 74 (2023).
28. Song, I. A., Oh, T. K. & Do, S. H. Trends in Perioperative Magnesium Sulfate Use in Patients Who Underwent Major Cancer Surgery: A Retrospective Population-Based Cohort Study in South Korea. *Cancer Control.* **30**, 10732748231180977 (2023).
29. Kumar, G. et al. Magnesium deficiency with high calcium-to-magnesium ratio promotes a metastatic phenotype in the CT26 colon cancer cell line. *Magnes Res.* **33**, 68–85 (2020).

Tables

Table 1 Demographic and clinical parameters according to MDS.

Variable	Total	MDS=0	MDS=1	MDS=2	MDS>=3	P value
Age(years)	44.72±0.38	37.27±0.46	46.49±0.47	54.46±0.73	65.41±1.23	< 0.0001
Age, n (%)						< 0.0001
<40 years	40.45(0.02)	59.70(1.93)	33.53(1.40)	16.64(2.27)	3.30(1.64)	
>=40 years	59.55(0.03)	40.30(1.93)	66.47(1.40)	83.36(2.27)	96.70(1.64)	
Race, n (%)						< 0.0001
Non-Hispanic White	73.72(0.05)	64.28(2.35)	78.31(2.04)	83.51(2.14)	87.41(2.20)	
Non-Hispanic Black	9.83(0.01)	12.02(1.67)	8.60(1.01)	7.79(1.22)	7.39(1.72)	
Mexican Ameirican	7.84(0.01)	11.83(1.25)	6.26(1.15)	2.95(0.70)	1.32(0.53)	
Other Race	8.60(0.01)	11.87(1.66)	6.83(1.27)	5.75(1.54)	3.88(1.80)	
Marital status, n (%)						< 0.001
Solitude	30.73(0.01)	34.50(1.85)	30.49(1.35)	24.38(2.12)	19.71(3.02)	
Cohabitation	69.16(0.04)	65.50(1.85)	69.51(1.35)	75.62(2.12)	80.29(3.02)	
PIR, n (%)						< 0.0001
1.3	16.01(0.01)	22.44(1.52)	14.01(1.29)	11.20(1.63)	8.75(1.74)	
1.3~3.5	33.86(0.02)	37.11(1.98)	34.54(1.48)	31.60(2.95)	44.66(4.06)	
≥3.5	45.14(0.02)	40.45(2.02)	51.45(1.88)	57.19(3.48)	46.58(4.41)	
BMI, n (%)						< 0.001
25kg/m2	29.20(0.02)	33.94(1.50)	28.22(1.24)	24.71(2.47)	18.27(2.52)	
25~30kg/m2	40.52(0.02)	36.49(1.75)	43.25(1.67)	47.35(2.23)	43.68(4.62)	
≥30kg/m2	28.89(0.01)	29.58(1.63)	28.53(1.19)	27.95(2.65)	38.05(3.43)	
Education level, n (%)						0.13
Less than or high school	43.85(0.03)	46.21(1.53)	41.89(1.71)	41.48(2.85)	47.97(4.90)	
Above high school	56.09(0.02)	53.79(1.53)	58.11(1.71)	58.52(2.85)	52.03(4.90)	
Smoking status, n (%)						< 0.0001
Never	42.90(0.02)	47.54(2.16)	42.17(1.72)	35.35(2.62)	31.69(3.79)	

Former	28.78(0.02)	21.34(1.31)	29.33(1.22)	40.46(2.55)	54.05(4.89)	
Current	28.30(0.02)	31.12(1.63)	28.50(1.29)	24.19(2.51)	14.25(3.50)	
Vigorous activity						< 0.0001
No	57.64(0.03)	54.86(1.76)	56.41(1.41)	64.05(2.72)	73.29(3.41)	
Yes	39.48(0.02)	44.17(1.83)	40.69(1.51)	29.90(2.02)	16.82(2.75)	
Unable to do activity	2.88(0.00)	0.96(0.24)	2.91(0.50)	6.05(1.32)	9.89(1.93)	
Moderate activity						< 0.0001
No	42.28(0.02)	44.89(1.67)	40.00(1.62)	40.51(2.57)	45.02(3.05)	
Yes	55.76(0.03)	54.26(1.63)	58.06(1.56)	56.30(2.83)	47.85(2.94)	
Unable to do activity	1.90(0.00)	0.85(0.23)	1.93(0.36)	3.18(1.02)	7.13(1.85)	
DM, n (%)						< 0.0001
No	89.62(0.04)	91.37(0.88)	91.24(0.85)	85.54(1.82)	72.36(3.29)	
Yes	10.38(0.01)	8.63(0.88)	8.76(0.85)	14.46(1.82)	27.64(3.29)	
CVD, n (%)						< 0.0001
No	90.96(0.04)	96.57(0.67)	92.19(0.69)	81.82(1.84)	58.89(4.05)	
Yes	9.02(0.01)	3.43(0.67)	7.81(0.69)	18.18(1.84)	41.11(4.05)	
Hypertension, n (%)						< 0.0001
No	65.53(0.03)	77.54(1.32)	65.51(2.06)	46.58(2.60)	19.45(3.33)	
Yes	34.33(0.02)	22.46(1.32)	34.49(2.06)	53.42(2.60)	80.55(3.33)	
Anemia, n (%)						< 0.0001
No	95.00(0.04)	99.02(0.24)	97.46(0.40)	95.99(0.78)	88.26(1.72)	
Yes	2.49(0.00)	0.98(0.24)	2.54(0.40)	4.01(0.78)	11.74(1.72)	
Cancer, n (%)						< 0.0001
No	93.56(0.04)	97.86(0.39)	93.05(0.59)	87.52(1.48)	79.83(2.20)	
Yes	6.37(0.01)	2.14(0.39)	6.95(0.59)	12.48(1.48)	20.17(2.20)	
MetS, n (%)						< 0.0001
No	74.66(0.03)	79.31(1.54)	76.31(1.23)	66.49(2.63)	43.99(4.28)	
Yes	25.34(0.02)	20.69(1.54)	23.69(1.23)	33.51(2.63)	56.01(4.28)	

ED, n (%)						< 0.0001
No	81.36(0.03)	89.83(0.85)	81.31(1.37)	70.27(2.00)	40.48(4.35)	
Yes	18.64(0.01)	10.17(0.85)	18.69(1.37)	29.73(2.00)	59.52(4.35)	
Magnesium intake(mg)	327.93±4.24	324.23± 5.75	339.38± 6.93	321.59± 6.62	280.23±10.60	< 0.001
Albumin (g/L)	43.83±0.08	44.22±0.11	43.82±0.09	43.21±0.20	42.45±0.25	< 0.0001
Total energy (kcal)	2666.63±25.49	2695.43±40.01	2735.59±46.58	2571.18±47.38	2098.63±65.44	< 0.0001

Values are mean +/- SD (continuous variables) or n% (categorical variables) are weighted.

Abbreviation: BMI=Body mass index, PIR=Poverty to income ratio, eGFR=estimated Glomerular Filtration Rate, PPI=Proton Pump Inhibitors DM=Diabetes mellitus, CVD=Cardiovascular disease, MetS=Metabolic syndrome, MDS=Magnesium Deficiency Scores.

Table 2 Association between MDS and ED.

Characteristic	crude model OR(95%CI)	Model 1 OR(95%CI)	Model 2 OR(95%CI)	Model 3 OR(95%CI)
MDS continue	2.11(1.88,2.36)	1.76(1.56,1.97)	1.62(1.44,1.84)	1.37(1.16,1.62)
MDS category				
0	ref	ref	ref	ref
1	2.03(1.58, 2.61)	1.67(1.27, 2.19)	1.58(1.19,2.10)	1.50(0.84, 2.66)
2	3.75(2.80, 5.04)	2.68(1.88, 3.81)	2.28(1.57,3.31)	1.78(0.87, 3.61)
>=3	12.99(8.47,19.91)	6.95(4.37,11.03)	5.50(3.41,8.90)	3.01(1.10, 8.21)
p for trend	<0.0001	<0.0001	<0.0001	0.01

Unadjusted model: no covariates were adjusted.

Model 1, age, race, marital status, education, FIR and BMI were adjusted.

Model 2, Model 1+alcohol intake, smoking status, vigorous and moderate activity were adjusted.

Model 3, Model 2+,DM, CVD, hypertension, CKD, cnemia, cancer, MetS, albumin, magnesium intake and energy were adjusted.

Table 3 Subgroup analysis of the association between MDS and ED.

Subgroup	MDS=0	MDS=1	MDS=2	MDS>=3	p for trend	P for interaction
CVD						0.4
No	ref	1.55(1.10,2.18)	1.91(1.28,2.84)	2.51(1.24,5.08)	0.001	
Yes	ref	1.63(0.54, 4.91)	2.07(0.45, 9.43)	7.91(2.09,29.92)	0.01	
DM						0.8
No	ref	1.52(1.13,2.05)	1.78(1.27,2.50)	3.44(2.00,5.91)	<0.001	
Yes	ref	1.74(0.78, 3.89)	2.85(1.04, 7.82)	3.34(0.78,14.38)	0.04	
Hypertension						0.2
No	ref	1.27(0.86, 1.88)	1.71(1.00, 2.91)	3.34(0.95,11.69)	0.01	
Yes	ref	2.16(1.42,3.28)	2.39(1.37,4.16)	4.08(2.32,7.16)	<0.001	
Anemia						0.41
No	ref	1.56(1.15,2.12)	2.00(1.39,2.90)	3.59(1.99,6.50)	<0.001	
Yes	ref	0.90(0.11, 7.67)	1.13(0.08, 16.73)	1.28(0.13, 13.17)	0.68	
Cancer						0.01
No	ref	1.39(1.00,1.93)	1.80(1.21,2.67)	3.68(1.83,7.41)	<0.001	
Yes	ref	9.89(1.58,62.12)	7.51(1.23,45.71)	7.34(1.01,53.02)	0.19	
MetS						0.53
No	ref	1.58(0.99,2.51)	1.73(0.92,3.27)	2.61(1.13,6.03)	0.04	
Yes	ref	1.55(1.07, 2.23)	2.07(1.35, 3.18)	4.56(2.08,10.03)	<0.001	
Dietary magnesium intake						0.93
Q1	ref	1.58(0.92,2.73)	2.63(1.57,4.40)	3.45(1.60,7.46)	<0.001	
Q2	ref	1.49(0.92,2.43)	1.74(0.99,3.03)	3.43(1.27,9.26)	0.01	
Q3	ref	1.45(0.69, 3.05)	1.40(0.57, 3.45)	3.26(1.01,10.56)	0.08	

Unadjusted model: no covariates were adjusted.

Model 1, age, race, marital status, education, FIR and BMI were adjusted.

Model 2, Model 1+alcohol intake, smoking status, vigorous and moderate activity were adjusted.

Model 3, Model 2+,DM, CVD, hypertension, CKD, Anemia, cancer, MetS, albumin, magnesium intake and energy were adjusted.

Analysis was stratified by diabetes, CVD , CKD, hypertension, cancer, anemia, MetS, and dietary magnesium intake, not adjusted for the stratification variable itself.

*means only in model 3.

Table 4 The Association of mortality with different statuses of MDS and ED.

Characteristic	Crude model HR(95%CI)	P value	Adjusted model HR(95%CI)	P value
Groups				
Group 0	ref		ref	
Group 1	2.10(1.66, 2.66)	<0.0001	1.19(0.88,1.61)	0.27
Group 2	3.38(2.24, 5.10)	<0.0001	1.00(0.60,1.68)	0.99
Group 3	11.13(8.85,13.99)	<0.0001	2.18(1.61,2.96)	<0.0001
p for trend	<0.0001		<0.0001	

Crude model: no covariates adjusted.

Adjusted model: adjusted for age, race, marital status, education, FIR and BMI, alcohol intake, smoking status, vigorous and moderate activity, DM, CVD, hypertension, Anemia, cancer, MetS, albumin, magnesium intake and energy.

Group 0: MDS=0 and non-ED; Group 1: MDS>0 and non-ED; Group 2: MDS=0 and ED; Group 3: MDS>0 and ED.

Table 5 The association between MDS and mortality in ED.

Characteristic	Crude model HR(95%CI)	P value	Adjusted model HR(95%CI)	P value
All-cause mortality				
MDS continue	1.60(1.42,1.79)	<0.0001	1.30(1.17,1.45)	<0.0001
MDS category				
0	ref		ref	ref
1	2.46(1.69,3.59)	<0.0001	1.98(1.22,3.21)	0.01
2	3.69(2.47,5.49)	<0.0001	2.61(1.58,4.30)	<0.001
>=3	5.51(3.51,8.64)	<0.0001	2.79(1.73,4.49)	<0.0001
p for trend	<0.0001		<0.0001	

Crude model: no covariates adjusted.

Adjusted model: adjusted for age, race, marital status, education, FIR and BMI, alcohol intake, smoking status, vigorous and moderate activity, DM, CVD, hypertension, Anemia, cancer, MetS, albumin, magnesium intake and energy.

Figures

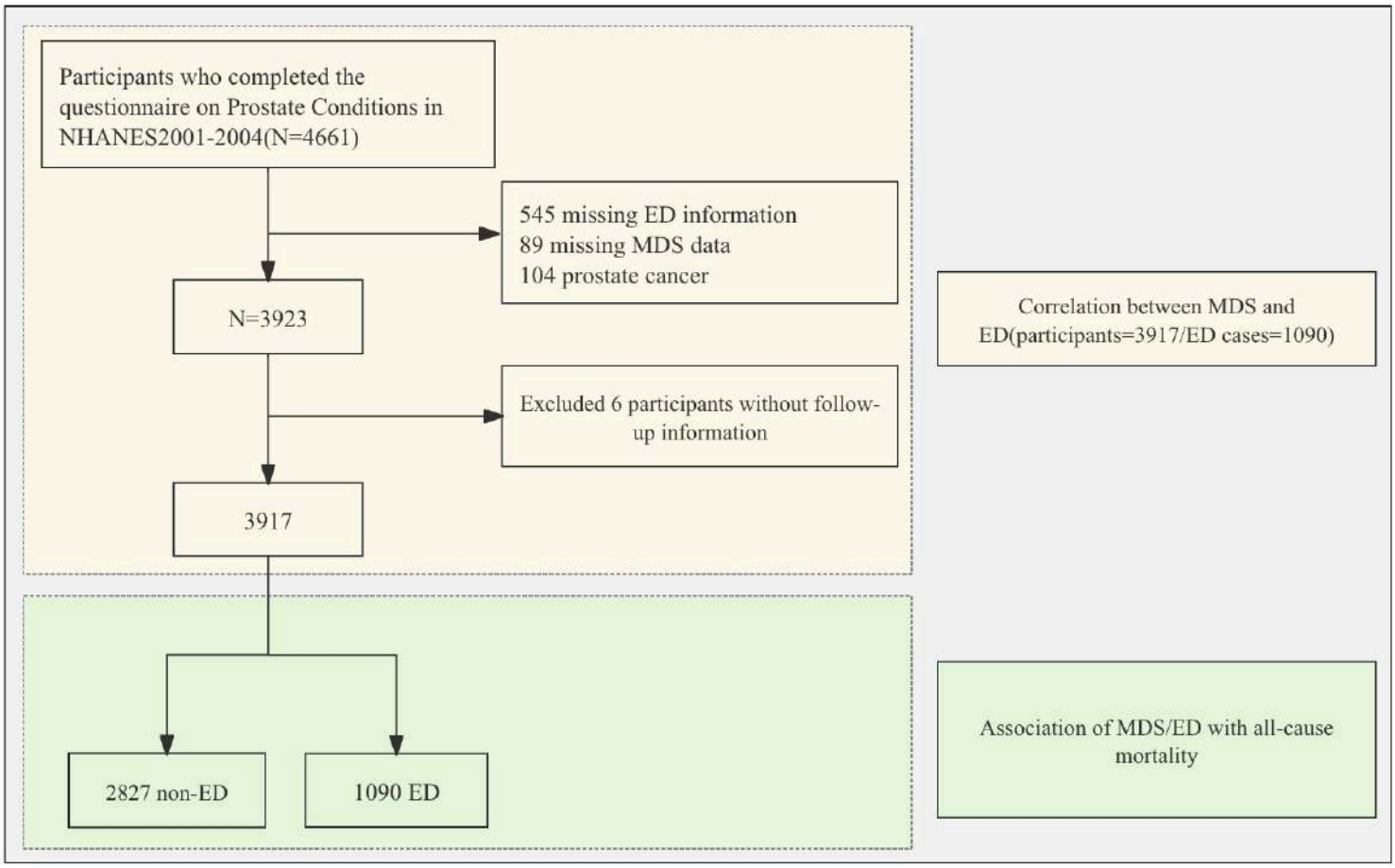

Figure 1

Flowchart of the sample selection from the National Health and Nutrition Examination Survey 2001 to 2004.

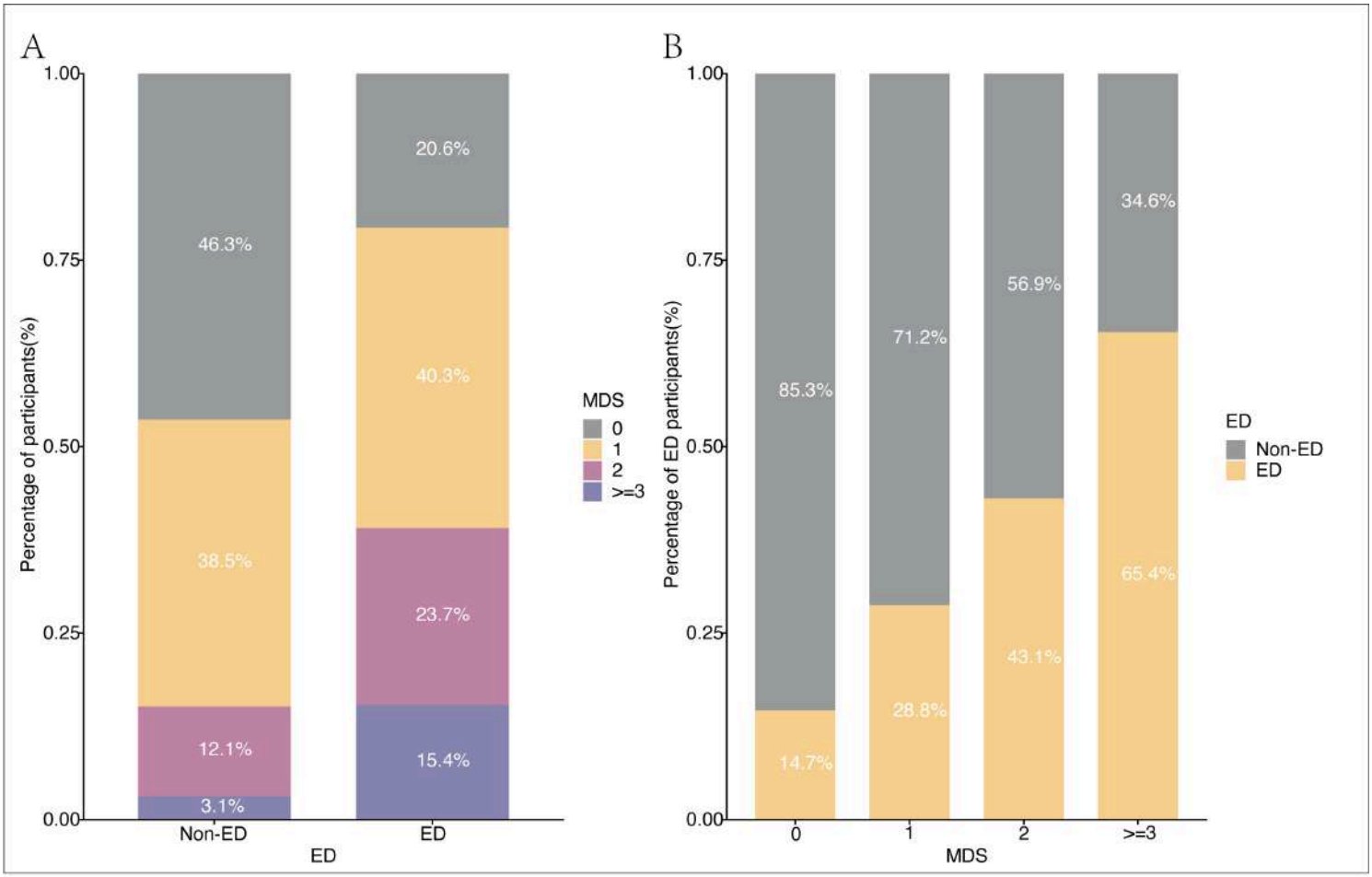

Figure 2

The distribution of MDS and ED in different groups. A: the MDS distribution in non-ED and ED groups. B: The non-ED and ED distribution in different MDS groups.

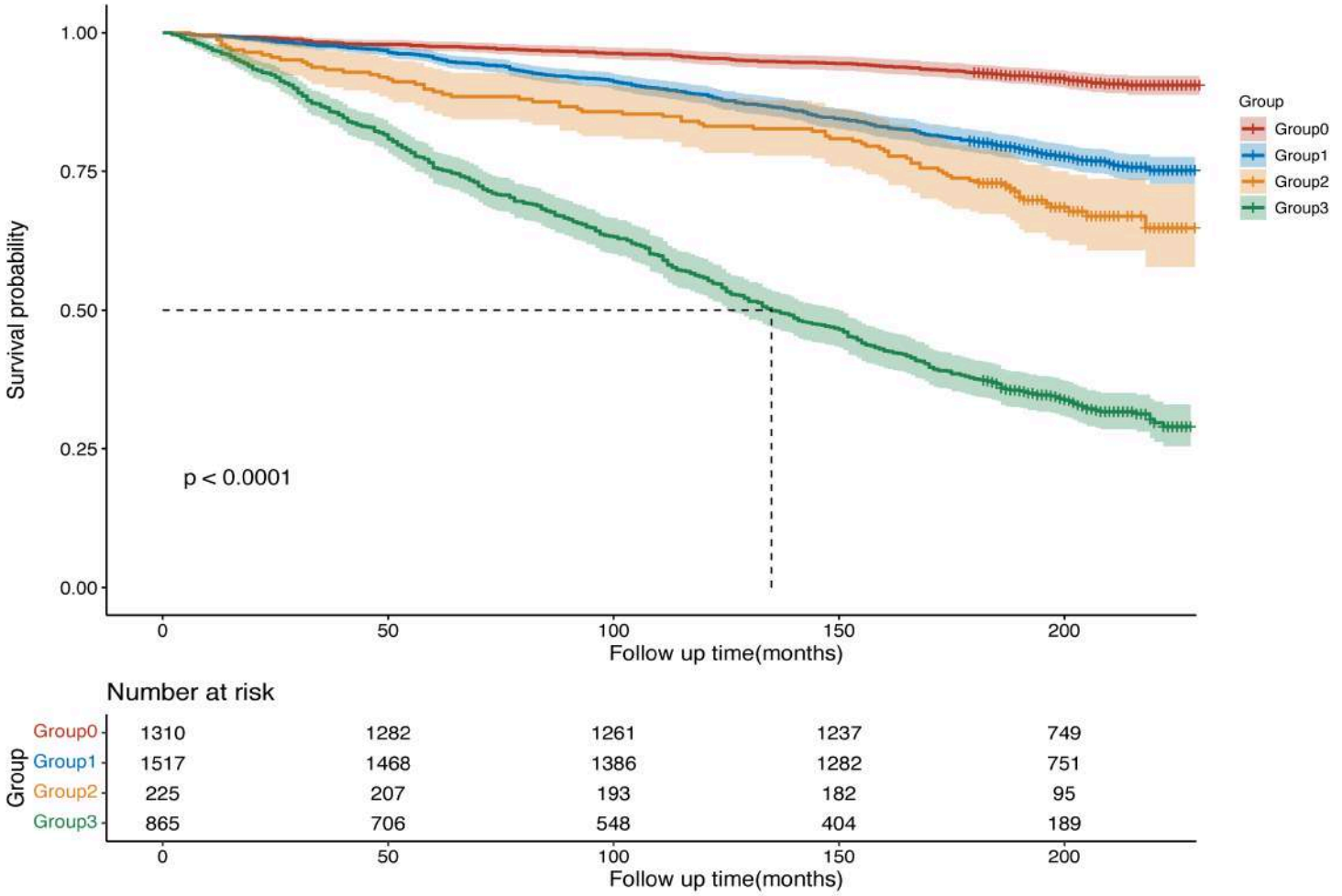

Figure 3

Kaplan-Meier curves were used to present the status of MDS and ED with all-cause mortality.

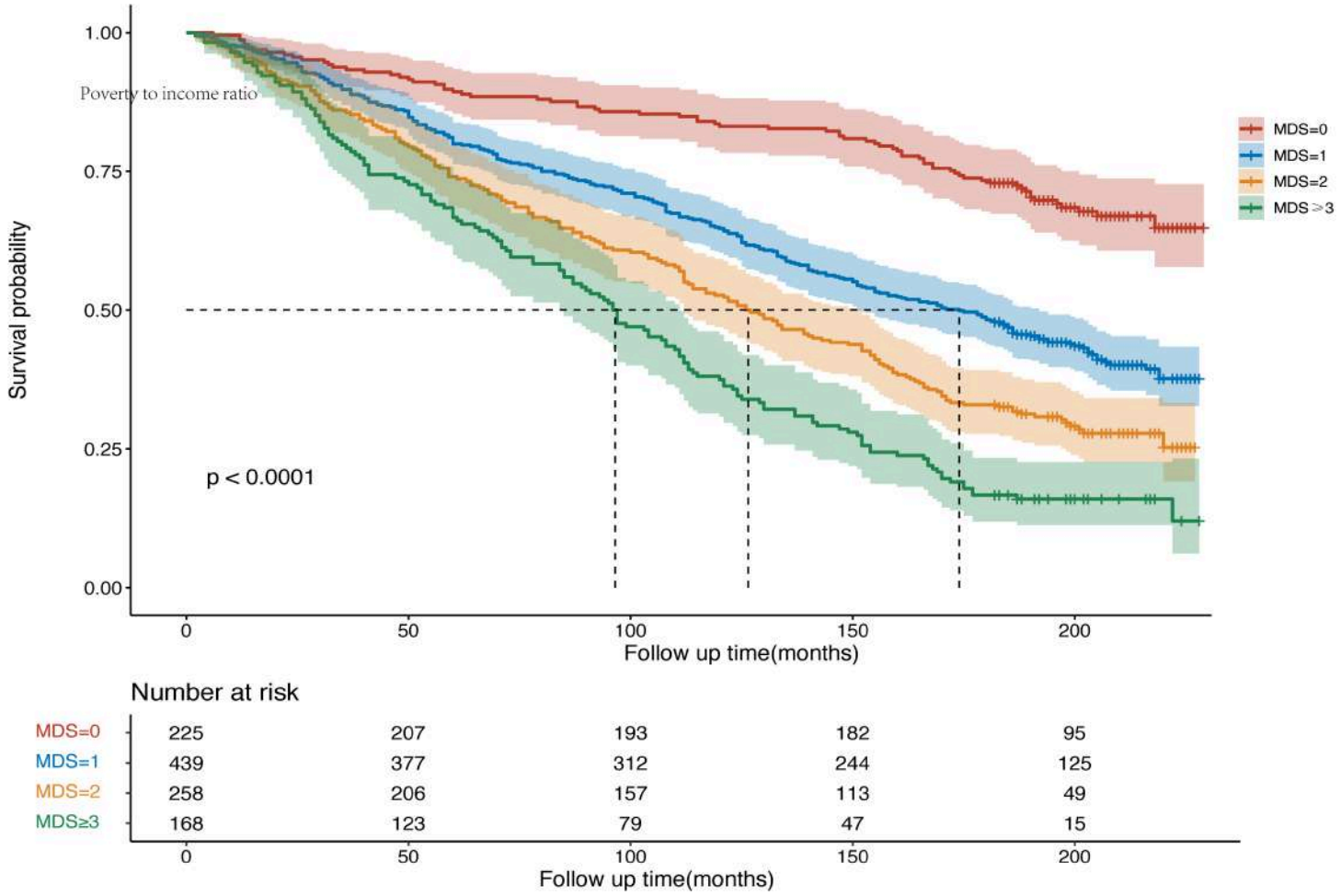

Figure 4

Kaplan-Maier cures were used to present the relationship of the MDS with all-cause mortality among participants with ED.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx