Multivitamin-mineral supplementation prevents acute upper respiratory tract infections

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ABSTRACT

Background and Objectives: Large-scale studies on the role of multivitamin-mineral (MVM) supplementation in preventing and managing acute respiratory infections (AURIs) are limited in Chinese populations. This study evaluated the impact of routine MVM use on AURI prevalence and symptom severity in a community-based Chinese cohort. **Methods and Study Design:** This retrospective study was conducted among community-based populations across China (n=3,415). Using a structured questionnaire, participants self-reported episodes of AURIs over three months. Based on regular use of MVM for at least 3 months, eligible participants were categorized into the MVM group and the control group. The impact of MVM on the frequency and severity of AURIs was assessed. Rigorous methodological approaches were applied to minimize potential biases. **Results:** The period prevalence of AURIs was significantly lower in the MVM group (29.9%) compared to controls (45.6%), odds ratio (OR) =0.508 (p<0.001). After propensity score matching, demographic and lifestyle factors were comparable between groups. The period prevalence of AURIs was 31.7% and 44.8% in the MVM and control groups (OR=0.572, p<0.001). Subgroup analysis indicated the protective effect of MVM supplementation was particularly significant among participants aged ≥45 years (OR=0.407, p<0.001). The MVM group reported lower prevalence of nasal congestion (OR=0.624, p<0.001), sore throat (OR=0.575, p<0.001), headache (OR=0.642, p<0.001), diarrhea (OR=0.718, 0.026), sneezing (OR=0.651, p=0.002), and fatigue (OR=0.694, p=0.004) relative to the control group. **Conclusions:** Daily MVM supplementation for at least 3 months reduced the period prevalence of the common cold and influenza and may contribute to enhanced immune resilience in the Chinese population.

Key Words: multivitamin-mineral supplementation, acute upper respiratory tract infections (AURIs), period prevalence, severity, real-world study

INTRODUCTION

Acute upper respiratory tract infections (AURIs) encompass a range of acute inflammatory conditions, predominantly viral or bacterial in origin, affecting the nasal passages, pharynx, or larynx. Viral etiologies account for approximately 70%~80% of cases and mainly include pathogens such as influenza viruses, parainfluenza viruses, respiratory syncytial virus (RSV), and adenoviruses. Influenza, in a broader sense, encompasses both common colds and flu, with distinct viral strains contributing to these presentations. The common cold is typically a self-limiting illness manifesting as nasal congestion, rhinorrhea, sore throat, and cough,

usually resolving within 10 days.[1, 2] In contrast, influenza symptoms, including acute febrile episodes, headache, generalized myalgia, malaise, and respiratory complaints, generally remit within 3-5 days, though residual nasal congestion, cough, and fatigue may persist beyond one week.[3-5] The influenza virus itself is highly transmissible and poses significant public health challenges due to its seasonal epidemic patterns worldwide.[6] Epidemiological studies indicate that adults aged 30-50 years old experience 2-3 colds annually,[7] and in China alone, approximately 3.4 million influenza-like illnesses are reported each year, contributing to an estimated 88,100 annual influenza-associated deaths.[8-10]

The immune system plays a pivotal role in pathogen detection and elimination, particularly against viral agents causing the common cold. Immune competence is closely correlated with susceptibility to episodic respiratory infections.[11] Essential micronutrients, including certain vitamins and minerals, significantly influence immune functionality and mucosal integrity.[12] Deficiencies in vitamins A, D, and E are linked to increased vulnerability to respiratory infections, with vitamin A deficiency specifically associated with immune dysregulation and heightened infection severity.[13-15] Antioxidants such as vitamin C protect immune cells and tissue from oxidative stress during the course of infection.[16-18] A meta-analysis assessing the impact of vitamins C, D, zinc, and multiple-micronutrient supplementation on the incidence and symptom duration of acute respiratory infections demonstrated that vitamin D supplementation effectively reduced acute respiratory infection risk and shortened the duration of symptoms and zinc supplementation did significantly reduced symptom duration.[19]

A typical broad-based daily multivitamin-mineral (MVM) supplement contains most or all essential vitamins and minerals at lower levels than individual supplements to meet the micronutrient needs and also to provide in quantities and forms that are more bioavailable.[20] In a study examining MVM supplementation in healthy older adults, 12 weeks of MVM supplement intake could diminish the severity and duration of illness episodes. However, significant change was not observed in immune status outcomes, such as salivary IgA and plasma cytokine/chemokine level.[11] A following randomized controlled trial evaluating micronutrient supplementation on common cold incidence, symptom duration, and severity found that the supplement group experienced fewer symptoms, such as runny nose, congestion, and cough, with shorter symptom duration compared to the placebo group.[21] Extensive research has been undertaken to understand the effects of these micronutrients, particularly vitamins C, D, and zinc, which are instrumental in modulating immune responses and mitigating the risk of respiratory infections. However, robust, real-world evidence on the

effectiveness of MVM supplementation for preventing common colds, alleviating symptoms, and reducing the number of episodes in large Chinese cohorts remains limited. Furthermore, prior large-scale studies have often utilized diverse MVM formulations from various manufacturers, introducing variability in nutrient composition and potentially impacting the reliability and generalizability of findings due to formulation heterogeneity, therefore, we utilized a standardized and well-recognized MVM supplement (Centrum or Centrum Silver) to minimize formulation variance and systematically assess its effects on the common cold, influenza period prevalence, and immune function within a substantial, real-world Chinese cohort.

In 2024, we conducted a large-scale, retrospective, real-world study to assess the effects of routine MVM supplementation on the period prevalence and symptom severity of AURIs, including common colds and influenza, across a community-based Chinese population. This study was conducted across diverse demographic groups in China, aiming to provide rigorous, evidence-based insights into the potential role of MVM supplementation in healthy Chinese populations.

MATERIALS AND METHODS

Study design

This retrospective, real-world study was conducted within a community-based Chinese population. The objective was to evaluate the impact of daily routine MVM supplementation on the period prevalence and symptomatology of AURIs, including common colds and influenza, among the healthy Chinese population. Participants were recruited through retail pharmacies in the community spanning 18 provinces in China by recruitment notification distributed by pharmacy staff. The inclusion criteria were: (1) age ≥18 years, no restrictions on gender; (2) daily routine use of Centrum or Centrum silver MVM or non-use of MVM supplement, where daily routine use was defined as consumption at least 4 days per week, with a minimum of one tablet per day for a duration of at least 3 months; (3) ability to comprehend and respond to the questionnaire; and (4) provision of informed consent. The exclusion criteria were: (1) presence of immune-related disorders or medication-induced immune suppression (e.g., use of glucocorticoids or other immunosuppressive agents); (2) use of other immunity-affecting supplements within the past six months (e.g., protein, fish oil or MVM supplements other than Centrum); (3) pregnancy or lactation; (4) history of gastrointestinal surgery, inflammatory bowel disease, malabsorption, or other gastrointestinal dysfunction; (5) participation in clinical trials within the previous 3 months; (6) inability to

understand and cooperate with investigations (7) initiation of MVM use after symptom onset for a respiratory infection, including common cold or influenza; and (8) refusal to participate in the study. Using a structured questionnaire, participants self-reported episodes of AURIs over three months. The questionnaire was completed in a single point in time and there was no follow-up. Based on self-reported regular use of MVM complexes for at least 3 months, eligible individuals were categorized into the MVM group; Non-users of MVM supplements were included in the control group. The study was approved by the Human Ethics Committee of Peking Union Medical College Hospital (Approval No. I-24PJ0205). All participants provided written informed consent. This study was registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR2400082242).

Study population and sampling

This study employed a community-based recruitment strategy that combined pharmacy-based convenience sampling. To ensure broad coverage across, the pharmacy covers 18 provinces in 6 major geographical regions of China (North, East, Central, South, Southwest, and Northwest of China). Provinces were selected based on geographical distribution and population density.

MVM supplements

MVM contents and processing methods affect nutrient absorption, which affects the result. To avoid bias, “Multivitamin with Multimineral Tablets (29)” or “Multivitamin with Multimineral Tablets (29-II)” were used in this study which is commercially available under the brand name “Centrum or Centrum Silver” in China. Key ingredients of the study products include vitamins A, C, E, and B-complex, along with critical minerals such as calcium, magnesium, and zinc, all integral to supporting physiological function. The complete formulation, detailing the individual ingredients and their concentrations, is presented in Supplementary Material 1.

Questionnaire development

In order to ensure the scientific robustness and practical applicability of the questionnaire, its development involved all study researchers and two additional experts with extensive experiences in the fields of epidemiology and health statistics. The expert panel provided feedback to refine the questionnaire, which was developed according to established methodological frameworks.[22] An anonymous feedback mechanism was employed during the

design process to minimize potential biases among expert opinions. After three rounds of expert consultation, the finalized questionnaire encompassed the following components: (1) Self-reported occurrence of AURIs, specifically common colds and influenza, over the prior three months. Respondents were encouraged to verify their responses through personal medical records or recall. Common colds were identified based on symptomatic presentation or personal medical records, while influenza was confirmed through medical documentation or self-reported positive influenza antigen tests; (2) Frequency, duration, and severity of specific symptoms. 'Severity of the symptoms' is judged based on the subjective feeling to the symptoms; Mild: Symptoms are noticed only with attention; Moderate: Symptoms are noticeable but do not affect work and life; Severe: Symptoms are very noticeable and affect work and life); (3) Work/school absenteeism attributed to AURI symptoms; (4) Occurrence of other infections; (5) Frequency of outpatient visits, emergency care, infusions, or hospitalizations; (6) Use of antibiotics; (7) Immune status, assessed using the validated Immune Status Questionnaire (ISQ), a widely used tool for measuring self-perceived immune health over the past year.[23] The ISQ is a 7-item questionnaire that assesses the frequency of immune-related symptoms, including common colds, diarrhea, headaches, muscle and joint pain, skin problems, and coughing. Each item is scored on a five-point Likert scale (Never = 0, Sometimes = 1, Regularly = 2, Often = 3, Almost Always = 4), with higher raw scores indicating poorer immune status. The final ISQ score is calculated by summing individual item scores and then translating the raw score into a standardized 0-10 scale, where higher final ISQ scores represent better immune health. A final ISQ score of ≥ 6 is generally indicative of good immune function.

In addition to general demographic information such as age and gender, data on past medical history were collected. Furthermore, participants reported their frequency and amount of consumption of various food groups, including vegetables, meat, aquatic products, fruit, and milk or soymilk, as well as alcohol intake over the past six months. The questionnaire was provided as Supplementary Material 2. Before formal data collection, the questionnaire underwent internal testing with a sample of 50 pre-screened participants who met the inclusion criteria but were not included in the study analysis. This preparatory testing assessed the questionnaire's content validity, with each expert panel member evaluating the content using the Item Content Validity Index (I-CVI), achieving an average index of 0.8 or higher. This process also confirmed the accuracy of data retrieval, transmission, and storage protocols, ensuring that the completed questionnaires maintained 100% alignment with the original entries.

Data collection

This study collected data by putting up posters, having people scan a code to fill out an electronic questionnaire or directly distributing a paper-based questionnaire by the pharmacies across 18 provinces of China. The potential participants who showed the intention to join the study were introduced to investigators and provided the inclusion/exclusion-related questions via internet-based communication software or phone calls. Twenty-five Investigators, who were consistently trained by the research team, screened, and verified each participant's eligibility according to the inclusion and exclusion criteria. Eligible individuals were instructed to complete a self-reporting questionnaire after they provided informed consent. By ticking the choices of 'whether the use of multivitamin minerals', 'frequency', and 'duration length' listed in the questionnaire, the participants can be divided into 2 groups: MVM group (regular MVM use) and control group (non-MVM use). Responses from electronic questionnaires were directly synchronized and stored in the study's electronic data capture (EDC) system, ensuring data integrity, logical verification, and traceability. The primary onsite quality check was conducted by investigators. For field responses obtained via paper questionnaires, investigators subsequently transferred the data into the electronic system. Both the electronic questionnaire interface and the EDC system were rigorously tested before study initiation to confirm usability and ensure data reliability. To ensure the accuracy of the data, for participants experiencing challenges with questionnaire completion, investigators provided support through telephone or on-site assistance, and responses were then recorded into the EDC system by the data collectors.

Outcomes

The primary outcome was the period prevalence of AURIs, specifically common cold and influenza, within the 3-month period preceding the survey. The period prevalence of AURIs, including cases of common cold and influenza, was assessed based on respondents' self-reported occurrences over the preceding three-month period, specifically between January 17, 2024, and July 12, 2024. Participants were instructed to report accurately, referencing either personal health records or recall. Instances of the common cold were identified by symptomatology or physician documentation, while influenza cases required verification either through physician-documented diagnosis or self-reported positive antibody testing for influenza antigens. The secondary outcomes were assessed over the same 3-month timeframe, which included: (1) period prevalence, duration, and severity of specific symptoms; (2) number of days absent from work or school due to AURI symptoms; (3) period prevalence of

additional infections; (4) frequency of outpatient, emergency, infusion, or hospitalization visits; (5) use of antibiotics; and (6) immune status.

Data quality control

Data quality assurance encompassed both automated and manual verification methods. Automated checks included: (1) identity validation via phone numbers; (2) prevention of duplicate submissions, with each phone number and IP address limited to a single submission; (3) detection of incomplete responses, excluding any questionnaire with missing data; (4) exclusion of responses with evident errors, such as implausible height or weight entries; and (5) identification of filling abnormalities, such as flagging questionnaires completed in an unreasonably short or lengthy duration. Manual quality checks involved traceability and logical verification of responses. During the study, researchers randomly selected 10% of completed questionnaires for telephone follow-up to confirm the authenticity of responses and the logical consistency of questionnaire completion. If inconsistencies were identified, the sampling proportion was progressively increased until all questionnaires were deemed reliable and logically sound.

Statistical analysis

All statistical analyses were conducted with R programming software. Hypothesis tests were primarily two-sided unless otherwise specified, with test statistics and associated *p*-values reported directly when employing Fisher's exact test. A significance threshold of $p<0.05$ was applied, and 95% confidence intervals (CIs) were used throughout. The analysis included two datasets: an unmatched sample dataset and a propensity score matched (PSM) dataset. All variables were characterized according to their data type. Qualitative variables were summarized as frequencies and percentages, while quantitative variables were presented with counts, means, standard deviations, medians, interquartile ranges (IQR), as well as minimum and maximum values. For comparisons, t-tests or Wilcoxon rank-sum tests were applied to continuous variables, chi-square tests or Fisher's exact tests to categorical data, and Wilcoxon rank-sum tests to ordinal data. To enhance baseline comparability between the MVM group and control group, PSM was applied using matching variables that included age, gender, ethnicity, educational background, average daily sleep duration, weekly exercise frequency, and average consumption of various food groups (vegetables, meat, aquatic products, fruit, and milk or soymilk), along with frequency of alcohol consumption within the last six months, although total energy intake was not directly measured in this study. PSM was performed at a

1:1 ratio, and analyses of differences in baseline characteristics, primary outcomes, and secondary outcomes between the two groups were conducted both before and after matching. Statistical results from both matched and unmatched datasets were reported. For both datasets, generalized linear models (GLMs) were utilized to assess differences in primary and secondary outcomes between groups. Two GLM variations were used for the unmatched data: one without covariate adjustments (Model 1) and another with covariate adjustments (Model 2). Covariates included age, gender, ethnicity, educational background, sleep duration, physical activity, and daily intake of vegetables, meat, aquatic products, fruit, milk, or milk powder. For the matched data, analysis was performed without covariate adjustments (Model 3). Subgroup analyses were also conducted based on participant age, with stratification by two age thresholds: 1) 18-44 years and ≥45 years; 2) 18-59 years and ≥60 years.

RESULTS

Basic characteristics of participants

Between April 17, 2024, and July 12, 2024, a total of 12,142 individuals expressed a willingness to participate in the study. Of these, 2,403 participants were excluded due to unsigned informed consent, incomplete or illogical questionnaire responses, duplicate submissions, or abnormal behaviors. The remaining 9,739 participants underwent further eligibility screening based on predefined inclusion and exclusion criteria. After this process, 3,453 individuals met the final inclusion criteria. Participants were categorized into two groups based on their self-reported use of MVM supplements. Individuals who reported regular use of Centrum or Centrum Silver for at least three months, with a frequency of at least four days per week, were assigned to the MVM group. Those who did not use any MVM supplements were classified as part of the control group. This resulted in 1,562 participants in the MVM group and 1,891 participants in the control group. Following data verification and quality control, 38 participants were excluded due to incomplete responses or loss of follow-up. As a result, the final analytic sample comprised 3,415 participants, including 1,549 in the MVM group and 1,866 in the control group. A study flowchart (Figure 1) provides a visual representation of the participant selection and retention process.

In the MVM group, there were 635 males (41.0%) and 914 females (59.0%), with a mean age of 43.5±15.9 years. In contrast, the control group included 902 males (48.3%) and 964 females (51.7%), with a mean age of 35.2±11.7 years old. Following PSM, 1,130 participants from each group were retained in the analysis, providing comparable demographic characteristics. In the matched MVM group, 484 (42.8%) were male and 646 (57.2%) were

female, with a mean age of 38.3±12.6 years old. The matched control group consisted of 488 males (43.19%) and 642 females (56.81%), with a mean age of 38.5±13.2 years old. Detailed baseline characteristics of the participants are provided in Table 1.

Prevalence of AURIs

A total of 463 cases (29.9%) of AURIs were reported in the MVM group, compared to 851 cases (45.6%) in the control group, demonstrating a significant difference in period prevalence between groups (OR=0.508, $p<0.001$). When adjusted for covariates, the odds ratio (OR) was 0.582 ($p<0.001$). Following PSM, the period prevalence of AURIs remained significantly lower in the MVM group, with 358 cases (31.7%) compared to 506 cases (44.8%) in the control group (OR=0.572, $p<0.001$). Detailed period prevalence data are presented in Table 2.

Subgroup analysis of AURIs period prevalence by age

For participants aged <60 years, 1,245 cases in the MVM group and 1,784 in the control group were analyzed. The period prevalence of AURIs was 32.8% in the MVM group compared to 46.1% in the control group, demonstrating a significantly lower period prevalence in the MVM group ($p<0.001$). In Model 1, the OR was 0.569 ($p<0.001$), and in Model 2, the OR was 0.595 ($p<0.001$). For those aged ≥60 years, 304 cases were identified in the MVM group and 82 in the control group, with period prevalence rates of 18.1% and 34.2%, respectively. This subgroup analysis indicated a significantly lower period prevalence in the MVM group than in controls (p=0.002), with Model 1 and Model 2 yielding ORs of 0.426 and 0.412, respectively ($p<0.01$; Table 3).

In participants aged <45 years, there were 935 cases in the MVM group and 1,499 cases in the control group, with period prevalence rates of 35.7% and 46.7%, respectively. This indicates a significantly lower period prevalence in the MVM group ($p<0.001$), with Model 1 showing an OR of 0.634 ($p<0.001$) and Model 2 an OR of 0.654 ($p<0.001$). For participants aged ≥45 years, there were 614 and 367 cases in MVM and control groups, and the period prevalence rate was 21.0% and 41.1%. This difference was statistically significant ($p<0.001$), with ORs of 0.380 and 0.407 in Models 1 and 2, respectively ($p<0.001$; Table 3).

Symptoms, duration, and severity of AURIs

Before PSM, analyses indicated statistically significant differences between the MVM and control groups regarding the period prevalence and severity of specific symptoms, including

fever, runny nose, nasal congestion, sore throat, cough, headache, diarrhea, sneezing, muscle aches, chills, and fatigue.

In terms of symptom period prevalence, the MVM group showed significantly reduced rates compared to the control group, including nasal congestion (68.0% vs. 78.1%, $p<0.001$), sore throat (63.3% vs. 75.4%, $p<0.001$), headache (46.4% vs. 58.4%, $p<0.001$), diarrhea (21.2% vs. 28.2%, $p=0.005$), sneezing (66.7% vs. 74.2%, $p=0.004$), and fatigue (56.4% vs. 66.5%, $p<0.001$). These differences remained statistically significant after adjustment using GLM, with results showing the following adjusted ORs for the MVM group relative to the control: nasal congestion (Model 1 OR=0.596, $p<0.001$; Model 2 OR=0.624, $p<0.001$), sore throat (Model 1 OR=0.552, $p<0.001$; Model 2 OR=0.575, $p<0.001$), headache (Model 1 OR=0.613, p<0.001; Model 2 OR=0.642, $p<0.001$), diarrhea (Model 1 OR=0.683, $p=0.005$; Model 2 OR=0.718, $p=0.026$), sneezing (Model 1 OR=0.713, p=0.007; Model 2 OR=0.651, $p=0.002$), and fatigue (Model 1 OR=0.665, p<0.001; Model 2 OR=0.694, $p=0.004$) (Table 4).

Regarding symptom severity, the MVM group reported a higher period prevalence of mild symptoms compared to the control group, with statistically significant differences for mild fever (81.6% vs. 74.7%, $p=0.037$), mild runny nose (74.4% vs. 68.0%, $p=0.031$), mild nasal congestion (71.8% vs. 63.6%, $p=0.011$), mild sore throat (72.7% vs. 64.2%, $p=0.005$), mild cough (73.0% vs. 65.8%, $p=0.009$), mild sneezing (82.2% vs. 74.0%, $p=0.009$), mild muscle pain (82.0% vs. 72.9%, $p=0.014$), and mild fatigue (74.7% vs. 68.6%, $p=0.045$) (Table 4). There was no statistically significant difference between the two groups concerning the duration of common cold or influenza symptoms ($p=0.866$) (Table 4).

ISQ score

Before PSM, 95.9% participants in the MVM group achieved an ISQ score of ≥6, whereas 90.7% in the control group ($p<0.001$). The OR in Model 1 was 2.41 ($p<0.001$), and in Model 2 the adjusted OR was 1.79, with statistical significance retained ($p<0.001$). After matching, differences in period prevalence of experiencing ISQ score ≥6 between the groups persisted, remaining statistically significant ($p=0.008$). With an OR of 1.636 in Model 3 ($p=0.009$) (Table 5). Overall, the MVM group demonstrated a higher proportion of participants with an ISQ score of ≥6, suggesting a potentially stronger immune profile within this cohort.

Other outcomes

Additional outcomes assessed included the number of school or workdays missed due to common cold and influenza symptoms within the pre-matched cohort, occurrence of other

infections, frequency of infusions, hospitalization duration for outpatient and emergency visits, and antimicrobial usage. No statistically significant differences were observed between the MVM and control groups for any of these parameters, with comprehensive data presented in Supplementary Material 3.

Safety

Adverse events were self-reported by participants through either electronic or paper-based questionnaires and subsequently recorded by the researchers. No severe adverse events were reported or recorded during the study period.

DISCUSSION

This large-scale, real-world study conducted in China was to test the effects of MVM supplementation on the period prevalence of common colds, influenza, and immune function. The study population exhibited notable diversity in geographical area, ethnicity, educational background, sleep duration, and exercise habits, ensuring a broad and representative enrollment of study subjects. According to the Report on Nutrition and Chronic Disease Status of the Chinese Population (2020), dietary patterns in China have shifted substantially alongside economic improvements, with a marked decline in vegetable and fruit intake, often replaced by calorie-dense, high-fat diets. Consequently, many individuals now face nutritional gaps, especially in vitamins and minerals. For instance, inadequate intake of calcium affects approximately 97.2% of the population, while shortage of vitamin B-2, vitamin B-1, vitamin A, and vitamin C affects 88.9%, 83.5%, 75.6%, and 68.9% of Chinese residents, respectively. 24 Existing literature underscores the critical and synergistic roles of multiple micronutrients, including vitamins and minerals, in sustaining immune function, with deficiencies linked to an increased susceptibility to infections.[17] Micronutrient supplements, such as vitamins C and D, have demonstrated both preventive and therapeutic benefits against AURIs, including influenza and the common cold, particularly when administered within optimal dose ranges.[21] Mechanism studies further elucidate that vitamin C enhances neutrophil activity and modulates inflammatory responses during infection,[25] while vitamin D supports immune defense by regulating antimicrobial peptides (e.g., defensins and cathelicidins) within immune cells.[17] Similarly, a recent systematic review conducted by Nault et al,[26] found that zinc supplementation may reduce the duration and symptom severity of the common cold because it is correlated with altered T helper cells balance, thymus activity, and response to the vaccine.

Multivitamins including vitamins A, B-6, B-12, C, D, E, and folate; and trace elements, including zinc, iron, selenium, magnesium, and copper, play important and complementary roles in supporting both the innate and adaptive immune systems. Deficiencies or suboptimal status in micronutrients negatively affect immune function and can decrease resistance to infections. Concerning innate immunity, the vitamins and minerals listed above collectively function to support the development and maintenance of physical barriers; production and activity of antimicrobial proteins; growth, differentiation, and motility/chemotaxis of innate cells; phagocytic and killing (e.g., oxidative burst) activities of neutrophils and macrophages; and promotion of and recovery from inflammation (e.g., cytokine production and antioxidant activity). They also support adaptive immunity, via lymphocyte differentiation, proliferation and homing; cytokine production; antibody production; and the generation of memory cells. It is not surprising, then, that deficiencies and even suboptimal status of these vitamins and minerals can impair immune functions. Depending on the deficient nutrient or nutrients, there can be decreases in the numbers of lymphocytes, impairment of phagocytosis and microbial killing by innate immune cells, altered production of cytokines, and reduced antibody responses. These functional impairments are, presumably, what lead to the clinical immune-related manifestations of deficiency, including infection and AURIs.[27] A large-scale study by Louca et al.,[28] conducted across the UK, USA, and Sweden, demonstrated that MVM supplementation reduced the risk of SARS-CoV-2 infection, an effect not observed with some single-nutrient supplements such as vitamin C.

Although micronutrients were proven to have key roles at every stage of the immune response and exhibit synergistic effects through complementary modes of action,[17] historical data on the efficacy of MVM supplements in preventing episodic infections have shown mixed results. For example, a 2020 review by Cramer et al.,[29] synthesizing seven studies on multivitamins for infection prevention, reported inconsistencies, concluding that MVM supplementation did not significantly reduce medical visits for influenza but could alleviate symptom severity during infection. Barringer et al.[30] found that among diabetic individuals, MVM supplementation significantly lowered infection rates (including upper respiratory tract infections, influenza-like syndrome, etc) (43% vs. 73%, $p<0.001$). Such variability in findings across studies may stem from small sample sizes or heterogeneity in MVM formulations.

Our findings from large-scale and real-world data indicate that individuals with daily routine use of MVM supplements for at least 3 months exhibit a significant reduction in the period prevalence of AURIs in a Chinese community-based healthy population, which provides robust evidence of the benefit of MVM supplements. The protective effect of MVM

supplementation was observed across the entire study population and remained statistically significant in age-stratified analyses. Although the period prevalence of AURIs was lower among older adults, likely due to reduced social interaction and lower exposure risk, this population remains particularly vulnerable to severe outcomes due to age-related immune decline (immune senescence), increased prevalence of chronic conditions, and higher susceptibility to complications.[31] These findings highlight the importance of targeted prevention strategies, particularly in older adults, to mitigate the risk of severe infection-related complications. Age-related immune senescence, along with nutritional status immune senescence, is characterized by dwindling production of T-cells and increased susceptibility to infections. Supplementation with essential vitamins and minerals has been shown to mitigate this decline, supporting immune function and consequently reducing respiratory infection risk.[32, 33] Many micronutrients in MVM have the synergistic effect on immunity functions either as regulators of molecular, cellular aspects of the immune response (e.g., iron, zinc, vitamin A, vitamin D) or together to support the specific anti-infection roles (e.g., zinc, vitamin D).[34] The synergistic effect between micronutrients was also known in the absorption aspect, such as Vitamin D promotes calcium absorption and Vitamin C promotes iron absorption. Then, these vitamins and minerals could be worked together to favorably modulate immune cell function, inflammatory responses, and infectious disease susceptibility and prognosis.[34] This is particularly important in older people, because many have generally poor nutritional status.

Beyond lowering the risk of AURIs, this study also found that individuals routinely taking MVM supplements experienced alleviated some of the AURIs symptoms compared to the control group, including fever, rhinorrhea, nasal congestion, sore throat, cough, headache, diarrhea, sneezing, myalgia, chills, and fatigue. Previous studies have demonstrated that immune support may be a central mechanism by which MVM supplementation reduces AURIs risk and attenuates symptom severity. For instance, Graat et al.[35] reported that vitamin E supplementation reduced symptom severity during episodic infections. Similarly, a study by Fantacone et al.[11] in an elderly cohort showed that 12 weeks of MVM supplementation increased serum levels of vitamin C and zinc, which correlated with reduced symptom severity during respiratory infections. Consistent with these findings, the present study observed significantly higher immune status scores in the MVM group compared to the control group, along with milder symptom severity during infection episodes. This result aligns with previous evidence supporting the immunomodulatory and symptom-alleviating effects of MVM supplementation. No adverse events were reported, which may be

attributable to the formulation's composition of vitamins and trace minerals, which are generally well-tolerated by the body at standard dosages. Most participants reported no significant discomfort when adhering to the recommended dosage.

AURIs are caused by a range of viral and bacterial pathogens, with seasonal variations influencing their prevalence and severity. Viral infections, such as influenza, RSV, and rhinoviruses, typically peak in colder months, while bacterial infections, including Streptococcus pneumoniae and Haemophilus influenzae, often follow viral illnesses as secondary infections.[36] MVM supplementation may help support immune function against both types of pathogens, as key nutrients such as vitamin C, vitamin D, and zinc have been shown to enhance innate immunity, antiviral defense, and mucosal integrity.[37,38] Seasonal deficiencies in these micronutrients, particularly in winter, may increase susceptibility to AURIs, making supplementation potentially more beneficial during this period. However, as our study relied on self-reported AURI cases without pathogen confirmation, it prevented a pathogen-specific analysis of MVM effectiveness. Future studies should incorporate microbiological diagnostics or serological testing to differentiate between viral and bacterial infections and assess whether MVM supplementation provides differential protection against specific AURI pathogens. Further research should also evaluate seasonal variations in supplement efficacy and determine optimal intake strategies for different population subgroups.

This study has several strengths. It is the first large-scale study in China to explore the effectiveness of MVM on the period prevalence and severity of AURI, encompassing diversity in age, gender, region, educational background, etc. In particular, results from subgroup analyses provide evidence for the benefits of MVM supplementation in different age groups. Secondly, in order to reduce the MVM formulation heterogeneity, this study utilized a standardized and well-recognized MVM supplement (Centrum) to minimize formulation variance. Thirdly, dietary and exercise data were also collected, accounting for variables such as daily intake of vegetables, meat, aquatic products, fruits, milk, or soymilk, frequency of alcohol consumption, and physical exercise. While baseline differences existed between the MVM and control groups, PSM minimized these discrepancies, rendering them statistically non-significant post-matching. This approach effectively reduced potential biases related to lifestyle factors, thus enhancing the scientific validity of our findings.

However, this study also has several limitations. First, as a retrospective and survey-based study, it relied on participants' self-reported data, which may be prone to recall bias or reporting inaccuracies. However, we endeavored to be as quantitative and specific as possible

for assessing the episode of AURI, symptom, and immune function assessment. Second, the cause of common colds and influenza is subject to seasonal variation, yet this study only collected data from January to July 2024, and the absence of pathogen-specific data limits our ability to establish a direct relationship between multivitamin supplementation and specific infectious agents. Future studies incorporating pathogen identification alongside micronutrient status assessment can provide a more comprehensive understanding of these interactions. Third, although we adjusted potential confounders using the PSM method, the absence of total energy and quantified micronutrient intake measurements may introduce residual confounding. Furthermore, our sampling approach and limited sample size may limit the representative of the data. Future studies can incorporate more comprehensive dietary assessments to provide a more detailed evaluation of total energy intake and micronutrient consumption. Lastly, the optimal intervention duration for MVM supplementation on AURI remained uncertain. Therefore, future research should emphasize long-term follow-up to elucidate the sustained impact of MVM on immune function.

This study provides the first large-scale, real-world evidence supporting the benefits of MVM supplementation in enhancing immune function, particularly in preventing AURIs, such as the common cold and influenza by 42.8%, and in alleviating symptoms among Chinese individuals with AURIs.

SUPPLEMENTARY TABLES AND FIGURES

The data supporting the results of this study are available upon request from the editorial office.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

AC, FD have disclosed that they are employees from Medical & Scientific Affairs of Haleon China R&D. FW, KY, WW, and YB, have no conflict of interest with Haleon China. The conflict of interest from all authors does not create a bias in the reporting of the results and conclusions.

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Table 1. Baseline demographic and characteristics of the study population[†]

Variables	Before PSM			After PSM		
	MVM group (N=1549)	Control group (N=1866)	*p*	MVM group (N=1130)	Control group (N=1130)	*p*
Age	43.5 ± 15.9	35.2± 11.7	<0.001[a]	38.3 ± 12.6	38.5 ± 13.2	0.984[a]
Gender			<0.001			0.865
Male	635 (41.0%)	902 (48.3%)		484 (42.8%)	488 (43.2%)	
Female	914 (59.0%)	964 (51.7%)		646 (57.2%)	642 (56.8%)	
Ethnic group			<0.001			0.911
Han ethnic group	1,504 (97.1%)	1,754 (94.0%)		1,088 (96.3%)	1,089 (96.4%)	
Others	45 (2.9%)	112 (6.0%)		42 (3.7%)	41 (3.6%)	
Height (cm)	165.70 ± 8.20	166.46 ± 8.74	0.013[a]	165.58 ± 8.47	166.28 ± 8.31	0.062[a]
Weight (kg)	63.69 ± 11.84	63.72 ± 12.67	0.776[a]	63.49 ± 12.26	64.03 ± 12.17	0.292[a]
BMI (kg/m^2)	23.10 ± 3.34	22.92 ± 3.91	0.005[a]	/	/	/
Educational background			0.014[a]			0.986[a]
Primary school	30 (1.9%)	15 (0.8%)		10 (0.9%)	9 (0.8%)	
Junior high school	101 (6.5%)	143 (7.7%)		72 (6.4%)	70 (6.2%)	
Secondary high school	329 (21.2%)	367 (19.7%)		216 (19.1%)	224 (19.8%)	
College/University	1,020 (65.9%)	1,240 (66. 5%)		780 (69.0%)	772 (68.3%)	
Graduates or above	69 (4.5%)	101 (5.4%)		52 (4.6%)	55 (4.9%)	
Hours of sleep per day			0.003[a]			0.928[a]
<6h	102 (6.6%)	96 (5.1%)		59 (5.2%)	61 (5.4%)	
6-8h	1,241 (80.1%)	1,464 (78.5%)		908 (80.4%)	906 (80.2%)	
>8h	206 (13.3%)	306 (16.4%)		163 (14.4%)	163 (14.4%)	
Weekly exercise (Running, swimming, playing ball, dancing, skipping rope, etc.)			0.003			0.569
No	385 (24.9%)	549 (29.4%)		309 (27.4%)	297 (26.3%)	
Yes	1,164 (75.1%)	1,317 (70.6%)		821 (72.6%)	833 (73.7%)	
Average weekly exercise frequency (more than 30 minutes in a single session)			<0.001[a]			<0.001[a]
Less than 1 time	46 (4.0%)	123 (9.3%)		69 (8.4%)	38 (4.5%)	
1-2 times	433 (37.2%)	680 (51.6%)		393 (47.9%)	353 (42.4%)	
3-4 times	336 (28.8%)	329 (25.0%)		223 (27.1%)	253 (30.4%)	
5 or more	349 (30.0%)	185 (14.1%)		136 (16.6%)	189 (22.7%)	
Average number of servings of vegetables per day (1 serving=100g)			<0.001			0.465
Barely	34 (2.2%)	85 (4.6%)		35 (3.1%)	32 (2.8%)	
1-2	974 (62.9%)	1,362 (73.0%)		781 (69.1%)	771 (68.2%)	
3-4	424 (27.4%)	340 (18.2%)		259 (22.9%)	264 (23.4%)	
5 or more	117 (7.5%)	79 (4.2%)		55 (4.9%)	63 (5.4%)	

MVM: multivitamin and mineral; PSM: propensity score matching

[†]Data are presented as mean ± standard deviation or number of subjects (percentage) [‡]by Wilcoxon rank-sum test. Rest was by Chi-square test

Table 1. Baseline demographic and characteristics of the study population[†] (cont.)

Variables	Before PSM			After PSM		
	MVM group (N=1549)	Control group (N=1866)	*p*	MVM group (N=1130)	Control group (N=1130)	*p*
Average number of servings of meat per day (1 serving=50g)			<0.001			0.684
Barely	53 (3.4%)	109 (5.8%)		43 (3.8%)	43 (3.8%)	
1-2	1,172 (75.7%)	1,443 (77.3%)		874 (77.4%)	865 (76.6%)	
3-4	284 (18.3%)	253 (13.56%)		180 (15.9%)	190 (16.8%)	
5 or more	40 (2.6%)	61 (3.3%)		33 (2.9%)	32 (2.8%)	
Times of aquatic products consumption per week			<0.001			0.566
None	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Once	665 (49.0%)	958 (63.4%)		547 (56.7%)	538 (55.4%)	
Twice	462 (34.0%)	426 (28.2%)		316 (32.8%)	326 (33.6%)	
3 times or more	231 (17.0%)	126 (8.3%)		102 (10.6%)	107 (11.0%)	
Average number of servings of fruit per day (1 serving=100g)			<0.001			0.281
Barely	111 (7.2%)	239 (12.8%)		98 (8.67%)	92 (8.2%)	
1-2	845 (54.5%)	976 (52.3%)		606 (53.6%)	590 (52.2%)	
3-4	409 (26.4%)	443 (23.7%)		296 (26.2%)	303 (26.8%)	
5 or more	184 (11.9%)	208 (11.2%)		130 (11.5%)	145 (12.8%)	
Average daily serving of milk or soymilk consumption (1 box=250 mL)			<0.001			0.971
Barely	346 (24.2%)	652 (37.7%)		297 (28.3%)	297 (28.7%)	
1 box	924 (64.8%)	909 (52.5%)		652 (62.2%)	638 (61.6%)	
1.5 boxes	157 (11.0%)	170 (9.8%)		99 (9.5%)	101 (9.7%)	
2 boxes or more	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Frequency of alcohol intaking			0.036			0.576
Barely	1,186 (89.0%)	1,346 (86.5%)		858 (89.9%)	855 (89.1%)	
1 time per week	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
2-3 times per week	104 (7.8%)	146 (9.4%)		70 (7.3%)	75 (7.8%)	
1-2 times per day	36 (2.7%)	43 (2.8%)		22 (2.3%)	25 (2.6%)	
3 or more times per day	6 (0.5%)	21 (1.3%)		5 (0.5%)	5 (0.5%)	

MVM: multivitamin and mineral; PSM: propensity score matching
[†]Data are presented as mean ± standard deviation or number of subjects (percentage)
[‡]by Wilcoxon rank-sum test. Rest was by Chi-square test

Table 2. Period prevalence of AURIs over three months

Outcome	Before PSM			Model 1		Model 2		After PSM			Model 3	
	MVM group (N=1549)	Control group (N=1866)	*p*	OR	*p*	OR	*p*	MVM group (N=1130)	Control group (N=1130)	*p*	OR	*p*
AURIs within 3 months			<0.001	0.508	<0.001	0.582	<0.001			<0.001	0.572	<0.001
No	1086 (70.1%)	1015 (54.4%)						772 (68.3%)	624 (55.2%)			
Yes	463 (29.9%)	851 (45.6%)						358 (31.7%)	506 (44.8%)			

AURIs: acute upper respiratory tract infections; MVM: multivitamin and mineral; PSM: propensity score matching; OR: odds ratio; GLM: generalized linear model.
Model 1: Pre-PSM, GLM without covariate adjustment; Model 2: Pre-PSM, GLM with covariate adjustment; Model 3: Post-PSM, GLM without covariate adjustment.

Table 3. Age-stratified subgroup analysis of AURIs period prevalence over a three-month period

Age Subgroups and AURIs within 3 months	Pre-PSM			Model 1		Model 2	
	MVM group (N=1549)	Control group (N=1866)	*p*	OR	*p*	OR	*p*
<60 years			<0.001	0.569	<0.001	0.595	<0.001
No	837 (67.2%)	961 (53.9%)					
Yes	408 (32.8%)	823 (46.1%)					
≥60 years			0.002	0.426	0.002	0.412	0.006
No	249 (81.9%)	54 (65.9%)					
Yes	55 (18.1%)	28 (34.2%)					
<45 years			<0.001	0.634	<0.001	0.654	<0.001
No	601 (64.3%)	799 (53.3%)					
Yes	334 (35.7%)	700 (46.7%)					
≥45 years			<0.001	0.38	<0.001	0.407	<0.001
No	485 (79.0%)	216 (58.9%)					
Yes	129 (21.0%)	151 (41.1%)					

AURIs: acute upper respiratory tract infections; MVM: multivitamin and mineral; PSM: propensity score matching; OR: odds ratio; GLM: generalized linear model.
Model 1: Pre-PSM, GLM without covariate adjustment; Model 2: Pre-PSM, GLM with covariate adjustment

Table 4. Specific symptoms, duration, and severity of AURIs

Outcomes	Pre-PSM			Model 1		Model 2	
	MVM group (N=463)	Control group (N=851)	*p*	OR	*p*	OR	*p*
Fever			0.193	0.847	0.147	0.868	0.258
Not experienced	229 (49.5%)	389 (45.7%)					
Experienced	234 (50.5%)	462 (54.3%)					
Severity of fever			0.037			0.738	0.153
Mild	191 (81.6%)	345 (74.7%)					
Moderate	38 (16.2%)	100 (21.6%)					
Severe	5 (2.2%)	17 (3.7%)					
Running nose			0.059	0.769	0.057	0.794	0.129
Not experienced	108 (23.3%)	161 (18.9%)					
Experienced	355 (76.7%)	690 (81.1%)					
Severity of running nose			0.031			0.795	0.15
Mild	264 (74.4%)	469 (68.0%)					
Moderate	79 (22.2%)	189 (27.4%)					
Severe	12 (3.4%)	32 (4.6%)					
Blocked nose			<0.001	0.596	<0.001	0.624	<0.001
Not experienced	148 (32.0%)	186 (21.9%)					
Experienced	315 (68.0%)	665 (78.1%)					
Severity of nasal congestion			0.011			0.773	0.11
Mild	226 (71.8%)	423 (63.6%)					
Moderate	73 (23.2%)	193 (29.0%)					
Severe	16 (5.0%)	49 (7.4%)					
Sore throat			<0.001	0.552	<0.001	0.575	<0.001
Not experienced	170 (36.7%)	209 (24.6%)					
Experienced	293 (63.3%)	642 (75.4%)					
Severity of sore throat			0.005			0.712	0.042
Mild	213 (72.7%)	412 (64.2%)					
Moderate	68 (23.2%)	171 (26.6%)					
Severe	12 (4.1%)	59 (9.2%)					
Cough			0.125	0.805	0.114	0.848	0.266
Not experienced	111 (24.0%)	173 (20.3%)					
Experienced	352 (76.0%)	678 (79.7%)					
Cough severity			0.009			0.75	0.066
Mild	257 (73.0%)	446 (65.8%)					
Moderate	79 (22.4%)	171 (25.2%)					
Severe	16 (4.6%)	61 (9.0%)					

MVM: multivitamin and mineral; PSM: propensity score matching; OR: odds ratio; GLM: generalized linear model.
Model 1: Pre-PSM, GLM without covariate adjustment; Model 2: Pre-PSM, GLM with covariate adjustment.

Table 4. Specific symptoms, duration, and severity of AURIs (cont.)

Outcomes	Pre-PSM			Model 1		Model 2	
	MVM group (N=463)	Control group (N=851)	*p*	OR	*p*	OR	*p*
Headache			<0.001	0.613	<0.001	0.642	<0.001
Not experienced	248 (53.6%)	354 (41.6%)					
Experienced	215 (46.4%)	497 (58.4%)					
Severity of headache			0.239			0.849	0.447
Mild	170 (79.1%)	375 (75.5%)					
Moderate	40 (18.6%)	97 (19.5%)					
Severe	5 (2.3%)	25 (5.0%)					
Diarrhea			0.005	0.683	0.005	0.718	0.026
Not experienced	365 (78.8%)	611 (71.8%)					
Experienced	98 (21.2%)	240 (28.2%)					
Severity of diarrhea			0.578			0.913	0.777
Mild	76 (77.6%)	180 (75.0%)					
Moderate	20 (20.4%)	51 (21.3%)					
Severe	2 (2.0%)	9 (3.7%)					
Sneeze			0.004	0.713	0.007	0.651	0.002
Not experienced	154 (33.3%)	220 (25.9%)					
Experienced	309 (66.7%)	631 (74.1%)					
Severity of sneezing			0.009			0.637	0.017
Mild	254 (82.2%)	467 (74.0%)					
Moderate	41 (13.3%)	139 (22.0%)					
Severe	14 (4.5%)	25 (4.0%)					
Muscle pain			0.857	0.976	0.832	0.987	0.917
Not experienced	263 (56.8%)	479 (56.3%)					
Experienced	200 (43.2%)	372 (43.7%)					
Severity of muscle pain			0.014			0.66	0.086
Mild	164 (82.0%)	271 (73.0%)					
Moderate	31 (15.5%)	84 (22.6%)					
Severe	5 (2.5%)	17 (4.6%)					
Chills			0.381	0.897	0.384	0.951	0.711
Not experienced	328 (70.8%)	583 (68.5%)					
Experienced	135 (29.2%)	268 (31.5%)					
Severity of chills			0.489			0.85	0.592
Mild	110 (81.5%)	210 (78.4%)					
Moderate	21 (15.5%)	51 (19.0%)					
Severe	4 (3.0%)	7 (2.6%)					

MVM: multivitamin and mineral; PSM: propensity score matching; OR: odds ratio; GLM: generalized linear model.
Model 1: Pre-PSM, GLM without covariate adjustment; Model 2: Pre-PSM, GLM with covariate adjustment.

Table 4. Specific symptoms, duration, and severity of AURIs (cont.)

Outcomes	Pre-PSM			Model 1		Model 2	
	MVM group (N=463)	Control group (N=851)	*p*	OR	*p*	OR	*p*
Fatigue			<0.001	0.665	<0.001	0.694	0.004
Not experienced	202 (43.6%)	285 (33.5%)					
Experienced	261 (56.4%)	566 (66.5%)					
Severity of fatigue			0.045			0.825	0.301
Mild	195 (74.7%)	388 (68.5%)					
Moderate	56 (21.5%)	134 (23.7%)					
Severe	10 (3.8%)	44 (7.8%)					
The entire duration of the cold			0.866			0.822	0.296
1-2 days	60 (13.0%)	103 (12.1%)					
3-4 days	229 (49.4%)	412 (48.4%)					
5-7 days	120 (26.0%)	225 (26.5%)					
More than 7 days	54 (11.6%)	111 (13.0%)					

MVM: multivitamin and mineral; PSM: propensity score matching; OR: odds ratio; GLM: generalized linear model.
Model 1: Pre-PSM, GLM without covariate adjustment; Model 2: Pre-PSM, GLM with covariate adjustment.

Table 5. Immune statues scores (ISQ)

	Pre-PSM			Model 1		Model 2		After PSM			Model 3	
Outcome	MVM group (N=1549)	Control group (N=1866)	*p*	OR	*p*	OR	*p*	MVM group (N=1130)	Control group (N=1130)	*p*	OR	*p*
ISQ score			<0.001	2.41	<0.001	1.79	<0.001			0.008	1.636	0.009
<6	63 (4.1%)	173 (9.3%)						49 (4.3%)	78 (6.9%)			
≥6	1486 (95.9%)	1693 (90.7%)						1081 (95.7%)	1052 (93.1%)			

MVM: multivitamin and mineral; PSM: propensity score matching; OR: odds ratio; GLM: generalized linear model. ISQ: Immune Status Questionnaire.
Model 1: Pre-PSM, GLM without covariate adjustment; Model 2: Pre-PSM, GLM with covariate adjustment

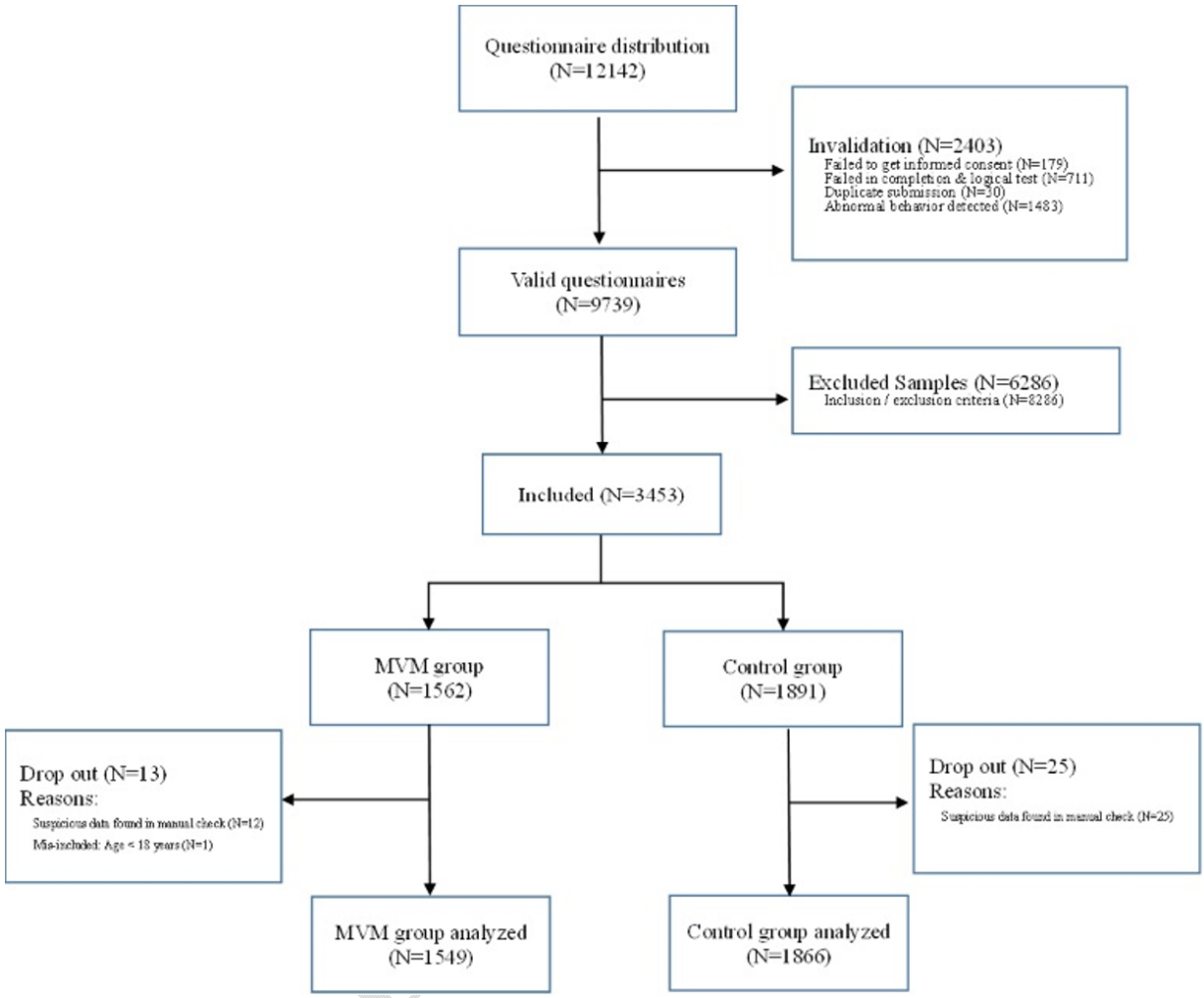

Figure 1. Flowchart illustrating study sample enrollment and inclusion.