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Association between submarine service and multi-morbidity among Korean naval personnel

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Contributorship statement

Dr. Jihun Kang (1st author) contributed to building the conception and design of the work, data collection, analyzing and interpretation of data and drafting and revising the article.

Prf. Yun-Mi Song(Corresponding author) contributed to building the conception and design of the work, analyzing and interpretation of data, clarifying important intellectual content of the result and critical revision from draft version to final version of the article.

Both authors participated in final approval of the version to be published and contributed to ensuing that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract

Objective: We aimed to estimate the prevalence of multi-morbidity (≥2 chronic health problems) among Korean submariners, and to evaluate the associations of submarine service with multi-morbidity and disease burden.

Study Design and Setting: This cross-sectional study included 590 naval personnel who visited a Korean primary care clinic during 2014–2015. Data regarding general characteristics and morbidities were collected from medical records, and disease burden was assessed using the Cumulative Illness Rating Scale (CIRS). Multiple logistic analysis was used to evaluate the associations of submarine service with multi-morbidity and disease burden.

Results: The prevalence of multi-morbidity were 11.7% among 180 non-submariners and 32.2% among 410 submariners. The prevalence of multi-morbidity and the CIRS scores gradually increased with age. Significant positive age-adjusted associations were found between the years of submarine service and multi-morbidity and high disease burden (CIRS score of ≥3)(P for trend < 0.001). These associations remained significant after adjusting for age, alcohol consumption, smoking status, and naval rank.

Conclusions: Submarine service was significantly associated with a higher risk of multi-morbidity and greater disease burden, compared to non-submarine service. This finding suggests that multi-dimensional and holistic healthcare approaches are needed for submariners.

Keywords: Submarine, multi-morbidity, disease burden

Article summary

Strengths and limitations of this study

This study investigated multi-morbidity and disease burden among submariners, who have unique characteristics and working environments.

We reviewed the data from medical records retrospectively and analyzed the association between service length in submarine and multi-morbidity and disease burden.

The cross-sectional design makes difficult to conclude the direction of causality regarding the relationship between submarine service and risk of multi-morbidity

The specificity of our study population, Korean submariners, would limit the generalization of our findings to other populations.

1. What is already known about this subject?

Multimorbidity (coexistence of ≥2 long-term diseases or medical conditions) is an increasing public health concern. Although various studies have evaluated multimorbidity among older individuals, no studies have evaluated multimorbidity among submariners, who have unique characteristics and working environments.

2. What are the new findings?

- A substantial proportion of submariners had multi-morbidity.

- Submarine service was associated with a higher risk of multi-morbidity, compared to non-submariner service.

- Submarine service was associated with a greater disease burden (assessed using the Cumulative Illness Rating Scale), compared to non-submarine service.

3.How might it impact on policy or clinical practice in the foreseeable future?

Multi-dimensional approaches and holistic healthcare are needed to manage the multiple medical conditions that submariners may experience.

INTRODUCTION

Multi-morbidity (the coexistence of ≥2 long-term diseases or medical conditions in one person) is associated with increased medical expenditures [1], decreased quality of life [2], and higher mortality [3]. With increasing life expectancy and population aging [4], multi-morbidity has become an important public health issue [5], because elderly people are likely to have multiple coexisting medical conditions. Therefore, most multi-morbidity research has been performed among older populations [3, 6], although multi-morbidity is not just an issue for elderly people [7]. A recent study found that >50% of people with multiple medical conditions were <65 years old [8], which implies that multi-morbidity should be investigated in a broader age range [9].

Military personnel are often relatively young people who perform physical training, military drilling, and deployment. Among military personnel, submariners complete a specialized selection process and training to ensure that they can complete their demanding duties. Therefore, submariners are considered a relatively healthy group at the time of their recruitment [10]. However, submariners are exposed to various environmental factors that can affect their health status, such as their confined work environment, physical inactivity, excessive caloric intake, circadian disruption, and isolation from family during deployment [11, 12]. Previous studies of submariners have revealed associations between these factors and increased risks of mortality or specific diseases [13, 14]. Nevertheless, little is known regarding the influence of submarine service on multi-morbidity.

Therefore, the present study aimed to estimate the prevalence of multi-morbidity among Korean submariners, and to evaluate the associations of submarine service with multi-morbidity and disease burden by comparing submariners and non-submarine naval personnel.

METHODS AND MATERIALS

Study design and participants

This cross-sectional retrospective study analyzed data from the medical records of naval personnel who visited a primary care facility at the military base in Jinhae (Republic of Korea) between April 2014 and March 2015. Among the 1,004 individuals who visited the clinic, we excluded 332 persons who had a temporary service commission and 82 persons with missing information regarding their socio-demographic characteristics (N = 15) or disease status (N = 67). Thus, 590 permanently commissioned naval personnel were ultimately included in the present study. We defined submariners as person who completed submarine training courses and worked in a submarine for ≥6 months, and categorized the subjects as either submariners (410 persons) or non-submariners (180 persons).

The study's retrospective protocol was approved and the requirement of informed consent was waived by the institutional review board of the Armed Forces Medical Command in Seongnam, South Korea (AFMC-15088-IRB-15-068).

Data collection

The subjects' socio-demographic data (age, years of submarine service, and naval rank), anthropometric data (height and weight), and health behaviors (smoking status and alcohol consumption) were obtained by reviewing their medical records. Body mass indexes (BMI, kg/m^2) were calculated as weight divided by height squared, and we defined obesity as a BMI of ≥25 kg/m^2 [15].

Co-existing chronic health problems were identified by reviewing the subjects' medical record and using a questionnaire regarding their medical history and symptoms, such as diabetes, chronic obstructive pulmonary disorder, asthma, hypertension, dyslipidemia, heart disease (congestive heart failure and ischemic heart disease), stroke, gastro-esophageal reflux, sleep apnea, arthritis, kidney disease, and psychological disorders. The presence of multi-morbidity (≥2 chronic medical conditions) was evaluated by counting the number of chronic health conditions that each subject had.

We estimated disease burdens based on the illnesses and their severities using the Cumulative Illness Rating Scale (CIRS) [16]. This tool assesses symptoms in 14 organ domains (cardiac; vascular; hematological; respiratory; eyes, ear, nose, and throat; upper gastrointestinal tract; lower gastrointestinal tract; hepatic and pancreatic; renal; genitourinary; musculoskeletal and tegumental; neurological; endocrine, metabolic, breast; and psychiatric). The CIRS was originally developed by Linn et al. [17] to assess chronic medical problems in a comprehensive manner, and was subsequently revised by Miller et al. [18] to measure common morbidities among elderly patients. This tool was later modified by Hudon et al. [16] to estimate multi-morbidity in the primary care setting, and was found to be a reliable and valid tool [2, 19, 20]. The CIRS score for each organ system ranges from 0 (no problems affecting that system) to 4 (extremely severe problems), and the total CIRS score is calculated by adding the scores for all 14 organ domains (range: 0–56). If a person currently smokes or has a high BMI (≥25 kg/m^2), then the person is considered to have disease burden in the respiratory and metabolic systems, respectively. The total CIRS score has a left-skewed distribution because it is very rare for a person to have severe medical conditions in every organ system.

Statistical analyses

The demographic characteristics, distributions of chronic health problems, and CIRS scores were compared between submariners and non-submariners using the chi-square test and t test, as appropriate. We also compared the distributions of chronic health problems and CIRS scores for three age strata, because the age distributions were significantly different between the submariners and non-submariners. We also evaluated the associations of submarine service with multi-morbidity and high disease burden using multiple logistic regression analysis after adjusting for age, alcohol consumption, smoking status, and naval rank (reference group: non-submariners with 0 years of submarine service). However, we did not include smoking status as a covariate in the model for disease burden, because it is a component of the CIRS score. All statistical analyses were performed using PASW Statistics software (version 21.0; SPSS Inc., Chicago, IL, USA). Two-tailed P-values of <0.05 were considered statistically significant.

RESULTS

Table 1 shows the subjects' characteristics. Compared to non-submariners, submariners were significantly older, were more likely to be a current smoker and obese, and had a higher naval rank ($p < 0.05$). Table 2 shows the distributions of chronic health problems and CIRS scores among all subjects and in the three age strata. The prevalences of multi-morbidity were 11.7% among non-submariners and 32.2% among submariners. The prevalence of multi-morbidity and the CIRS scores gradually increased with age among both submariners and non-submariners. In all age strata, the number of chronic health problems consistently tended to higher among submariners, compared to among non-submariners. The mean CIRS score for submariners was higher than that of non-submariners in all age groups.

Table 3 shows the adjusted associations of submarine service with the risks of multi-morbidity and high disease burden (CIRS of ≥3). With increasing years of submarine service, the risk of having multi-morbidity and high disease burden (CIRS score of ≥3) tended to increase (P for trend < 0.001).. This association remained significant after adjusting for age, alcohol consumption, smoking status, and naval rank.

Supplementary Table 1 shows the prevalences of symptoms in each CIRS organ domain. Compared to non-submariners, submariners more frequently experienced symptoms in the vascular, respiratory, ear/nose/throat, and endocrine domains. Both groups had similar prevalences of symptoms in the cardiac, upper and lower gastrointestinal, musculoskeletal or tegumental, and neurological domains.

DISCUSSION

The present study is the first study to examine the prevalence of multi-morbidity and disease burden among submariners. Use of the CIRS score allowed us to provide more comprehensive data, especially regarding the disease burden, compared to previous studies. Based on our findings, approximately 30% of submariners had multi-morbidity, and this rate was approximately 3× greater than the prevalence among non-submariner naval personnel (11.7%). The higher rate of multi-morbidity among submariners was consistently observed in different age strata, which suggests that the significant difference in the multi-morbidity rate was not caused by different age distributions.

It is difficult to compare the prevalence of multi-morbidity between different studies, as they have varying definitions and methods for assessing multi-morbidity. However, a previous study has confirmed that multi-morbidity prevalence is comparable between studies when multi-morbidity is defined as ≥2 disease entities, regardless of the specific disease entity definitions in each study [21]. Nevertheless, the prevalence of multi-morbidity varies according to study. When we exclude elderly subjects (to simplify the age-based comparisons), we found that the prevalence of multi-morbidity among non-submariners was 11.7%, which was lower than the reported prevalences in the Netherlands (24.2% among 20–59-year-old men from the general population) [22], Scotland (20.5% among 25–65-year-old men from the general population) [8], and Canada (20.4% among 18–64-year-old men from the general population) [23].

In the present study, submariners more frequently experienced symptoms in the vascular, respiratory, and endocrine CIRS domains, compared to non-submariners (Supplementary Table 1). This finding is partially consistent with the findings of a previous study, which revealed that respiratory infections and elevated blood pressure without a hypertension diagnosis were common morbidities among American submariners [24]. We assume that our findings may be related to the fact that current smoking and obesity are counted as respiratory and endocrine diseases, respectively, in the CIRS system [16]. When we excluded current smokers and obese subjects from each CIRS domain, a significant difference was observed in the endocrine domain ($P < 0.001$), although no significant difference was observed in the respiratory domain (data not shown).

Among both non-submariners and submariners, we observed positive associations between age and multi-morbidity, and this association has been clearly documented in previous studies [6, 8, 22]. In addition, our finding of increasing disease burden (estimated using CIRS) with age was similar to the findings from a Canadian study [19]. However, submariners had a greater prevalence of multi-morbidity and greater disease burden in all age groups, compared to non-submariners. Although the current smoking rate among submariners was comparable with that among the general population of Korean men (47% in 2012) [25], the higher smoking rate among submariners may explain their greater disease burden, as current smoking is considered a respiratory problem in the CIRS system. In addition, the submariners' obesity rate was higher than that among Korean non-submariners, American small submarine crews (17.9% in 2011) [26], and American police officers and firefighters (30.7% in 2002) [27], which may also explain the difference in disease burden. Unfortunately, the confined submarine environment is not conducive to vigorous activity and exercise during deployment [28], and submariners’ caloric intake tends to exceed their expenditure during this time [12]. Thus, the combination of low physical activity levels and excessive caloric intake may elevate the risk of accumulating abdominal and visceral fat [29], which could explain the prevalence of obesity among submariners. These factors may have contributed to the high disease burden and prevalence of multi-morbidity among submariners, compared to non-submariners.

The present study also revealed that the duration of submarine service was positively associated with the prevalence of multi-morbidity. As age is strongly associated with multi-morbidity [8, 22], it may be possible that the association between multi-morbidity and service years was confounded by age. However, after adjusting for age, the positive association between service years and multi-morbidity was only slightly attenuated and remained statistically significant. Thus, our findings do not support a confounding effect of age on the association of service years with multi-morbidity.

Submariners are exposed to several health risk factors, such as *Helicobacter pylori* infection related to overcrowding and extremely limited sanitary facilities [30], increased cortisol levels related to chronic stress state and sleep deprivation [31], and a high rate of smoking. These risks might have cumulative negative effects on submariners' health status, which might partially explain the higher prevalence of multi-morbidity in this population. Nevertheless, previous studies have reported conflicting findings regarding the health of submariners. For example, a study by the American Navy revealed that submarine duty did not increase the risk of hospitalization in 16 major diagnostic categories and submarine-associated diagnoses (infective and parasitic diseases [tuberculosis, viral hepatitis, mononucleosis, venereal diseases], neoplasms, endocrine and nutritional diseases [diabetes mellitus], hematological diseases, mental disorders [alcohol abuse, drug abuse, schizophrenia, affective disorders, personality disorders], nervous system diseases, cardiovascular diseases [essential hypertension, myocardial infarct, chronic ischemic heart disease], respiratory diseases [acute upper respiratory infection, influenza, pneumonia, asthma], digestive system diseases [dental diseases], genito-urinary diseases [kidney and ureteral stones], skin diseases, musculoskeletal diseases, congenital anomalies, accidents and poisoning [fracture, concussion, sprain, contusion], and unspecified diseases and supplemental findings) [32]. However, we could not directly compare the findings of that study and our study, as we used different methods to identify morbidities (outpatient clinical records vs. hospitalization records and multi-morbidity vs. single disease entities).

Few studies have evaluated the risk of mortality among submariners, and those studies have reported no significant association. A British study of Royal Naval submarine crews concluded that working in a submarine was not associated with increased cancer mortality, although the authors detected an increase in liver cirrhosis-related mortality that might not be attributable to the submarine environment [14]. A Norwegian study also failed to detect differences in all-cause mortality among surface vessel and submarine crews, and the submariners had a lower rate of all-cause mortality, compared to the general population of Norwegian men [13]. Several explanations were proposed for the null finding from the Norwegian study. First, the participants had relatively low mean service times (2.7 years), which may have been insufficient to noticeably affect the subjects' mortality. Another plausible explanation is that morbidity may not significantly affect mortality in a relatively young and healthy population, unlike older populations [3]. Furthermore, the "healthy soldier effect" may result in submariners having a good initial health state, as military personnel and submariners are specially selected to perform challenging tasks, which could diminish the adverse effects of the submarine working environment [10].

There are several limitations in the present study. First, the cross-sectional design precludes any conclusions regarding the causality of the relationship between submarine service and risk of multi-morbidity. However, it seems logical to assume that submarine work increases multi-morbidity, rather than vice versa, because it is very unlikely that multi-morbidity would drive an individual to submarine work. Second, the absence of a standardized definition led us to create our own arbitrary definition for multi-morbidity (≥2 coexisting chronic conditions in a single patient), and it is possible that we underestimated or overestimated the prevalence of multi-morbidity. Third, the specificity of our study population (Korean submariners) would limit the generalization of our findings to other populations.

In conclusion, this Korean study revealed that, compared to non-submarine service, submarine service was significantly associated with a higher risk of multi-morbidity and greater disease burden, even after adjusting for relevant covariates. These findings suggest that scrupulous attention is needed to assess submariners and manage their health conditions in multi-dimensional and holistic ways. Further research is needed to examine the effects of multi-morbidity on disease patterns, quality of life, and overall mortality among submariners.

Conflicts of interest: None.

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Table 1. General and clinical characteristics of study subjects

	Overall (N=590)	Non-submariner (N=180)	Submariner (N=410)	P-value*
Age, years, mean (SD)	33.2(8.5)	31.2(9.9)	34.1(7.7)	<0.001
Height, cm	173.8(0.1)	173.4(0.1)	174.0(0.1)	0.189
Body mass index, kg/m^2, mean (SD)	25.0(3.0)	24.3(3.0)	25.3(2.9)	<0.001
≥25 kg/m^2, N(%)	267(45.3)	63(35.0)	204(49.8)	0.001
18.5-24.9 kg/m^2, N(%)	322(54.6)	116(64.4)	206(50.2)	
<18.5 kg/m^2, N(%)	1(0.2)	1(0.6)	0(0)	
Alcohol consumption, N(%)	487(82.5)	152(84.4)	335(81.7)	0.420
Current smoker, N(%)	277(46.9)	68(37.8)	209(51.0)	0.003
Job-Ranking, N(%)				<0001
Officer	103(17.5)	31(17.2)	72(17.6)	
Petty officer	465(78.8)	127(70.6)	338(82.4)	
Others	22(3.7)	22(12.2)	0(0%)	
Mean (SD) years of service in submarine	NA	0	7.1(5.3)	NA

N: number of subjects, SD: standard deviation, NA: not applicable

* P-value was obtained by t test for continuous variables and chi-square test for categorical variable

Table 2. Comparison of the number of chronic health problems and mean Cumulative Illness Rating Scale score between submariners and non-submariners by age group

	Overall			<30 years			30-39 years			≥40 years		
	Non-submariner	Sub mariner	P-value*	Non-submariner	Sub mariner	P-value*	Non-submariner	Sub mariner	P-value*	Non-submariner	Sub mariner	P-value*
Chronic health problems, N (%)												
0	96(53.3)	126(30.7)	<0.001	62(61.4)	56(44.8)	0.009	17(51.5)	52(27.8)	0.012	17(37.0)	18(18.4)	0.005
1	63(35.0)	152(37.1)		33(32.7)	47(37.6)		12(36.4)	75(40.1)		18(39.1)	30(30.6)	
2	21(11.7)	132(32.2)		6(5.9)	22(17.6)		4(12.1)	60(32.1)		11(23.9)	50(51.0)	
Cumulative Illness Rating Scale score, mean(SD)												
	1.66(1.16)	2.35(1.51)	<0.001	1.31(1.03)	1.70(1.23)	0.010	1.64(1.0)	2.33(1.43)	0.008	2.43(1.21)	3.23(1.59)	0.003

N: number, SD: standard deviation

* P-value was obtained by chi-square test or t-test

Table 3. Association of submarine service with the risk of multi-morbidity† and high disease burden‡

	Years of submarine service				
	0 year (N=180)	1-4 years (N=158)	5-9 years (N=107)	≥10 years (N=145)	P_{trend}¶
OR (95% CI)* for the association with multi-morbidity †					
Model 1	1	3.46(1.75-6.87)	2.59(1.37-4.89)	3.97(2.19-7.19)	<0.001
Model 2	1	3.97(1.91-8.25)	2.75(1.41-5.38)	3.78(2.06-6.94)	<0.001
OR (95% CI)* for the association with the high disease burden‡ estimated by Cumulative Illness Rating Scale					
Model 1	1	1.86(1.04-3.32)	2.36(1.37-4.05)	2.77(1.63-4.71)	0.001
Model 2	1	2.00(1.09-3.67)	2.23(1.24-4.01)	1.97(1.09-3.57)	0.028

OR (95% CI): odds ratio (95% confidence interval)

* estimated by multiple logistic regression analysis. In model 1, age was adjusted. In model 2, age, alcohol intake, smoking status (not included in the analysis for the disease burden), and job-ranking were adjusted.

† defined as two or more chronic health problems in a person

‡ defined as Cumulative Illness Rating Scale score ≥ 3 ¶ assessed by linear regression analysis, for which year of service was put in the model as a continuous variable.

Supplementary Table 1. Distribution of symptoms in each organ domain of Cumulative Illness Rating Scale

Organ domains	Non-submariner N(%)	Submariner N(%)	P-value*
Overall	84(46.7)	284(69.3)	<0.001
Cardiac	2(1.1)	4(1.0)	0.880
Vascular	21(11.7)	125(30.5)	<0.001
Respiratory	74(41.1)	239(58.3)	<0.001
Eyes ear, nose, and throat	53(29.4)	85(20.7)	0.021
Upper gastrointestinal tract	5(2.8)	8(2.0)	0.529
Lower gastrointestinal tract	9(5.0)	12(2.9)	0.211
Musculoskeletal or tegumental	34(18.9)	96(23.4)	0.222
Neurological	5(2.8)	11(2.7)	0.948
Endocrine, metabolic, breast	63(35.0)	211(51.5)	<0.001
Other organ	4(2.2)	19(4.6)	0.163

N: number, SD: standard deviation

* P-value was obtained by chi-square test or t-test

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The association between submarine service and multi-morbidity: a cross-sectional study in Korean naval personnel

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Contributorship statements

Dr. Jihun Kang (1st author) conceived of and designed the study; collected, analyzed, and interpreted the data; and wrote and revised the report. Prof. Yun-Mi Song (corresponding author) conceived of and designed the study; collected, analyzed, and interpreted the data; and provided important intellectual context and critical revisions for the report. Both authors have approved the final version for publication, and accepted responsibility for the accuracy and integrity of the data and the analysis.

ABSTRACT

Objective: We aimed to estimate the prevalence of multi-morbidity (≥2 chronic health problems) among Korean submariners, and to evaluate the associations of submarine service with multi-morbidity and disease burden.

Study Design and Setting: This cross-sectional study included 590 naval personnel who visited a Korean primary care clinic during 2014–2015. Data regarding general characteristics and morbidities were collected from medical records, and disease burden was assessed using the Cumulative Illness Rating Scale (CIRS). Multiple logistic regression analysis was used to evaluate the associations of submarine service with multi-morbidity and disease burden.

Results: The prevalence of multi-morbidity was 11.7% among 180 non-submariners and 32.2% among 410 submariners. The prevalence of multi-morbidity and the CIRS scores gradually increased with age. Significant positive age-adjusted associations were observed between the overall years of submarine service and multi-morbidity or high disease burden (a CIRS score of ≥3) (P for trend < 0.001). These associations remained significant after adjusting for age, alcohol consumption, smoking status, and naval rank.

Conclusions: Submarine service was significantly associated with a higher risk of multi-morbidity and greater disease burden, compared to non-submarine service. This finding suggests that multi-dimensional and holistic healthcare approaches are needed for submariners.

Keywords: Submarine, multi-morbidity, disease burden, occupational exposure

Strengths and limitations of this study

Multi-morbidity as well as disease burden of submariners were evaluated.

The cross-sectional design precludes any conclusions regarding the direction of causality in the relationship between submarine service and multi-morbidity.

The specificity of our study population, Korean submariners, limits the generalization of our findings to other populations.

INTRODUCTION

Multi-morbidity (the coexistence of ≥2 long-term diseases or medical conditions in one person) is associated with increased medical expenditures [1], decreased quality of life [2], and higher mortality [3]. With increasing life expectancy and population aging [4], multi-morbidity has become an important public health issue [5], because elderly people are likely to have multiple coexisting medical conditions. Therefore, most multi-morbidity research has been performed among older populations [3 6], although multi-morbidity is not just an issue for elderly people [7]. A recent study found that >50% of people with multiple medical conditions were <65 years old [8], which implies that multi-morbidity should be investigated in a broader age range [9].

Military personnel are often relatively young people who perform physical training, military drilling, and deployment. Among military personnel, submariners are a unique population because they complete a specialized selection process and training to ensure that they can perform their demanding duties. Thus, submariners are considered a relatively healthy group at the time of their recruitment [10]. However, submariners are concurrently exposed to various environmental risk factors that can affect their health status, such as their confined work environment, physical inactivity, excessive caloric intake, circadian disruption, and isolation from family during deployment [11-13]. Few studies of submariners have evaluated the effects of these occupational risk factors on submariners' health status with controversial findings. A Norwegian study revealed that submariners had increased risks of bladder cancer and non-melanoma skin cancer[14]. Similarly, a

German study revealed that submariners had a higher rate of *Helicobacter pylori* infection, compared to other naval personnel [15]. On the other hand,, a British study revealed that submarine service was not associated with increased risks of mortality or specific diseases [16]. Moreover, little is known whether submarine service is associated with multi-morbidity. Therefore, the present study aimed to estimate the prevalence of multi-morbidity among Korean submariners, and to evaluate the associations of submarine service with multi-morbidity and disease burden by comparing submariners and non-submarine naval personnel.

METHODS AND MATERIALS

Study design and participants

This cross-sectional study analyzed data from the medical records of naval personnel who visited a primary care facility at the military base in Jinhae (Republic of Korea) between April 2014 and March 2015. Among the 1,004 male individuals who visited the clinic, we excluded 332 persons who had a temporary service commission (conscripted individuals who were not eligible for submariner service) and 82 persons with missing information regarding their socio-demographic characteristics (N = 15) or disease status (N = 67). Thus, 590 permanently commissioned naval personnel who volunteered for professional naval service were ultimately included in the present study. We defined submariners as person who completed submarine training courses and worked in a submarine for ≥6 months, and categorized the subjects as either submariners (410 persons) or non-submariners (180 persons).

The study's protocol complied with the STROBE guidelines. In addition, the protocol was approved and the requirement of informed consent was waived, by the institutional review board of the Armed Forces Medical Command in Seongnam, South Korea (AFMC-15088-IRB-15-068).

Data collection

The subjects' socio-demographic data (age, years of submarine service, and naval rank), anthropometric data (height and weight), and health behaviors (smoking status and alcohol consumption) were obtained by reviewing their medical records. Current smokers were defined individuals who had smoked >100 cigarettes during their life and were currently smoking. Self-reporting was used to identify individuals who consumed alcohol. Body mass indexes (BMI, kg/m^2) were calculated as weight divided by height squared, and we defined obesity as a BMI of ≥25 kg/m^2, based on the definition for the Korean population [17].

We identified co-existing chronic health problems in several ways. First, we asked the study subjects to answer "yes" or "no" to each question regarding whether they had experienced or had received treatment for the chronic conditions such as such as diabetes, chronic obstructive pulmonary disorder, asthma, hypertension, dyslipidemia, heart disease (congestive heart failure and ischemic heart disease), stroke, gastro-esophageal reflux, sleep apnea, arthritis, kidney disease, or psychological disorders, using a self-administered questionnaire. Then, an additional physician-led examination was followed to identify any unreported conditions. In addition, we reviewed medical record of each study subjects. Because an electronic medical record system was implemented in 2013, we reviewed the medical records as far as that point and data extraction from the subjects' medical records was performed using disease codes from the 10th revision of the International Classification of Disease. The presence of multi-morbidity (≥2 chronic medical conditions) was evaluated by counting the number of chronic health conditions that each subject had.

We estimated disease burdens based on the illnesses and their severities using the Cumulative Illness Rating Scale (CIRS) [18]. This tool assesses symptoms in 14 organ domains (cardiac; vascular; hematological; respiratory; eyes, ear, nose, and throat; upper gastrointestinal tract; lower gastrointestinal tract; hepatic and pancreatic; renal; genitourinary; musculoskeletal and tegumental; neurological; endocrine, metabolic, breast; and psychiatric). The CIRS was originally developed by Linn et al. [19] to assess chronic medical problems in a comprehensive manner, and was subsequently revised by Miller et al. [20] to measure common morbidities among elderly patients. This tool was later modified by Hudon et al. [18] to estimate multi-morbidity in the primary care setting, and was found to be a reliable and valid tool [2 21 22]. The CIRS score for each organ system ranges from 0 (no problems affecting that system) to 4 (extremely severe problems), and the total CIRS score is calculated by adding the scores for all 14 organ domains (range: 0–56). If a person currently smokes or has a high BMI (≥25 kg/m^2), then the person is considered to have disease burden in the respiratory and metabolic systems, respectively. The total CIRS score has a left-skewed distribution because it is very rare for a person to have severe medical conditions in every organ system.

Statistical analyses

The demographic characteristics, distributions of chronic health problems, and CIRS scores were compared between submariners and non-submariners using the chi-square test and t test, as appropriate. We also compared the distributions of chronic health problems and CIRS scores for three age strata (<30 years, 30–39 years, and ≥40 years) because the age distributions were significantly different between the submariners and non-submariners. There is no standardized cut-off value for high disease burden based on CIRS score, and we arbitrarily defined subjects in the upper tertile of CIRS scores (≥3) as having high disease burden. We also evaluated the associations of submarine service with multi-morbidity and high disease burden using multiple logistic regression analysis after adjusting for age, alcohol consumption, smoking status, and naval rank (reference group: non-submariners with 0 years of submarine service). However, we did not include smoking status as a covariate in the model for disease burden, because it is a component of the CIRS score. All statistical analyses were performed using PASW Statistics software (version 21.0; SPSS Inc., Chicago, IL, USA). Two-tailed P-values of <0.05 were considered statistically significant.

RESULTS

Table 1 shows the subjects' characteristics. Compared to non-submariners, submariners were significantly older, were more likely to be a current smoker and obese, and had a higher naval rank ($p < 0.05$). Table 2 shows the distributions of chronic health problems and CIRS scores among all subjects and in the three age strata. The prevalence of multi-morbidity were 11.7% among non-submariners and 32.2% among submariners. The prevalence of multi-morbidity and the CIRS scores gradually increased with age among both submariners and non-submariners. The number of chronic health problems and CIRS scores were significantly higher among submariners, compared to those among non-submariners, across all age groups.

Table 3 shows the adjusted associations of submarine service with the risks of multi-morbidity and high disease burden (CIRS of ≥3). Submarine service of one-year or longer was positively associated with multi-morbidity and disease burden as compared with less than one-year of submarine service. This association remained significant after adjusting for age, alcohol consumption, smoking status, and naval rank. However, a dose-response relationship according to submarine service duration was not evident (Supplementary Table 1).

Supplementary Table 2 shows the prevalence of symptoms in each CIRS organ domain. Compared to non-submariners, submariners more frequently experienced symptoms in the vascular, respiratory, ear/nose/throat, and endocrine domains. Both groups had similar prevalences of symptoms in the cardiac, upper and lower gastrointestinal, musculoskeletal or tegumental, and neurological domains. When we excluded current smokers and obese subjects from the CIRS domain analyses, no significant difference was observed in the endocrine and respiratory domain.

DISCUSSION

The present study is the first to examine the prevalence of multi-morbidity and disease burden among submariners. Use of the CIRS score allowed us to provide more comprehensive data, especially regarding the disease burden, compared to previous studies [3 8 23]. Based on our findings, approximately 30% of submariners had multi-morbidity, and this rate was approximately 3 times greater than the prevalence among non-submariner naval personnel (11.7%). The higher rate of multi-morbidity among submariners was consistently observed in different age strata, which suggests that the significant difference in the multi-morbidity rate was not caused by different age distributions.

A previous study in primary care setting has shown that multi-morbidity prevalence might be comparable between studies when multi-morbidity is defined as ≥2 disease entities, regardless of the specific disease entity definitions in each study [24]. The prevalence of multi-morbidity varies according to study. After excluding elderly subjects (to simplify the age-based comparisons), we found that the prevalence of multi-morbidity among non-submariners was 11.7%, which was lower than the reported prevalence in the Netherlands (24.2% among 20–59-year-old men from the general population) [23], Scotland (20.5% among 25–65-year-old men from the general population) [8], and Canada (20.4% among 18–64-year-old men from the general population) [25].

However, the difference in the prevalence of multi-morbidity across studies might have been causes from the varying definitions and methods for assessing multi-morbidity, and study setting.

In the present study, submariners more frequently experienced symptoms in the vascular, respiratory, endocrine, and ear/nose/throat CIRS domains, compared to non-submariners (Supplementary Table 2). This finding is partially consistent with the findings of a previous study, which revealed that respiratory infections and elevated blood pressure without a hypertension diagnosis were common morbidities among American submariners [26]. We assume that our findings may be related to the fact that current smoking and obesity are counted as respiratory and endocrine diseases, respectively, in the CIRS system [18]. Although smoking rate was lower in submariners than in non-submariners, worse air quality from enclosed space of submarine might have contributed to the more prevalent respiratory and ear/nose/throat symptoms.

We observed positive associations between age and multi-morbidity among both non-submariners and submariners, and this association has been clearly documented in previous studies [6 8 23]. In addition, our finding of increasing disease burden (estimated using CIRS) with age was similar to the findings from a Canadian study [21]. However, submariners had a greater prevalence of multi-morbidity and greater disease burden in all age groups, compared to non-submariners. Although the current smoking rate among submariners was comparable to that among the general population of Korean men (47% in 2012) [27], the higher smoking rate among submariners may explain their greater disease burden, as current smoking is considered a respiratory problem in the CIRS system. In addition, the submariners' obesity rate was higher than that among Korean non-submariners, American small submarine crews (17.9% in 2011) [28], and American police officers and firefighters (30.7% in 2002) [29], which may also explain the difference in disease burden. Although different cut-off values for obesity are used for Korean and American populations (≥25 kg/m^2 vs. ≥30 kg/m^2), we think the results are comparable in terms of obesity diagnoses because Asian populations have a higher body fat composition for any given BMI, compared to Caucasian populations [30] and increased all-cause mortality is associated with BMI of ≥25 kg/m^2 in the Korean population [31].

Unfortunately, the confined submarine environment is not conducive to vigorous activity and exercise during deployment [32], and submariners' caloric intake tends to exceed their expenditure during this time [12]. Moreover, submariners' shift work schedules during their deployment may increase their risk of metabolic syndrome [33]. Thus, the combination of low physical activity levels, excessive caloric intake, and circadian misalignment may elevate the risk of accumulating abdominal and visceral fat [34], which could explain the prevalence of obesity among submariners. These factors may also have contributed to the high disease burden and prevalence of multi-morbidity among submariners, compared to non-submariners.

As age is strongly associated with multi-morbidity [8 23], it is possible that the association between multi-morbidity and service years was confounded by age. However, after adjusting for age, the positive associations of submarine service with multi-morbidity as well as disease burden were only slightly attenuated. Thus, our findings negate a significant confounding effect of age on the association.

Submariners are exposed to several health risk factors, such as *Helicobacter pylori* infection, that are related to overcrowding and extremely limited sanitary facilities [15], increased cortisol levels related to chronic stress state and sleep deprivation [35], and low air quality in an enclosed space [36]. These risk factors may have cumulative negative effects on submariners' health status, which might partially explain the higher prevalence of multi-morbidity in this population. Nevertheless, previous studies have reported conflicting findings regarding the health of submariners. For example, a study by the American Navy revealed that submarine duty did not increase the risk of hospitalization for 16 major diagnostic categories and submarine-associated diagnoses [37]. However, we could not directly compare the findings of that study and our study, as we used different methods to identify morbidities (outpatient clinical records vs. hospitalization records and multi-morbidity vs. single disease entities).

Few studies have evaluated the risk of mortality among submariners, and those studies have reported no significant association. A British study of Royal Navy submarine crews concluded that working in a submarine was not associated with increased cancer mortality, although the authors detected an increase in liver cirrhosis-related mortality that might not be attributable to the submarine environment [16]. A Norwegian study also failed to detect differences in all-cause mortality among surface vessel and submarine crews, and the submariners had a lower rate of all-cause mortality, compared to the general population of Norwegian men [14]. Several explanations were proposed for the null finding from the Norwegian study. First, the participants had relatively low mean service times (2.7 years), which may have been insufficient to noticeably affect the subjects' mortality. Another plausible explanation is that morbidity may not significantly affect mortality in a relatively young and healthy population, unlike older populations [3]. Furthermore, the "healthy soldier effect" may result in submariners having a good initial health state, as military personnel and submariners are specially selected to perform challenging tasks, which could diminish the adverse effects of the submarine working environment [10].

There are several limitations in the present study. First, the cross-sectional design precludes any conclusions regarding the causality of the relationship between submarine service and risk of multi-morbidity. However, it seems logical to assume that submarine work increases multi-morbidity, rather than vice versa, because it is very unlikely that multi-morbidity would drive an individual to submarine work. Second, the absence of a standardized definition led us to create our own arbitrary definition for multi-morbidity (≥2 coexisting chronic conditions in a single patient), and it is possible that we underestimated or overestimated the prevalence of multi-morbidity. Third, selection bias is possible, as it was not possible to blind the physicians to the personnel's status as submariners or non-submariners. In addition, subjects who visited the clinic may have had a relatively poor health status, compared to other naval personnel who did not seek medical attention. Fourth, the specificity of our study population (Korean submariners), and the absence of an age-matched non-navy personnel control group, may limit the generalization of our findings to other populations.

In conclusion, this Korean study revealed that, compared to non-submarine service, submarine service was significantly associated with a higher risk of multi-morbidity and greater disease burden, even after adjusting for relevant covariates. These findings suggest that scrupulous attention is needed to assess submariners and manage their health conditions in multi-dimensional and holistic ways. Further research is needed to examine the effects of multi-morbidity on disease patterns, quality of life, and overall mortality among submariners.

Conflicts of interest: None.

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Table 1. General and clinical characteristics of study subjects

	Overall (N=590)	Non-submariner (N=180)	Submariner (N=410)	P-value*
Age, years, mean (SD)	33.2(8.5)	31.2(9.9)	34.1(7.7)	<0.001
Height, cm	173.8(0.1)	173.4(0.1)	174.0(0.1)	0.189
Body mass index, kg/m^2, mean (SD)	25.0(3.0)	24.3(3.0)	25.3(2.9)	<0.001
≥25 kg/m^2, N(%)	267(45.3)	63(35.0)	204(49.8)	0.001
18.5-24.9 kg/m^2, N(%)	322(54.6)	116(64.4)	206(50.2)	
<18.5 kg/m^2, N(%)	1(0.2)	1(0.6)	0(0)	
Alcohol consumption, N(%)	487(82.5)	152(84.4)	335(81.7)	0.420
Current smoker, N(%)	277(46.9)	68(37.8)	209(51.0)	0.003
Job-Ranking, N(%)				<0001
Officer	103(17.5)	31(17.2)	72(17.6)	
Petty officer	465(78.8)	127(70.6)	338(82.4)	
Navy civilian	22(3.7)	22(12.2)	0(0%)	
Mean (SD) years of service in submarine	NA	0	7.1(5.3)	NA

N: number of subjects, SD: standard deviation, NA: not applicable

* P-value was obtained by t test for continuous variables and chi-square test for categorical variable

Table 2. Comparison of the number of chronic health problems and mean Cumulative Illness Rating Scale score between submariners and non-submariners by age group

	Overall			<30 years			30-39 years			≥40 years		
	Non-submariner	Sub mariner	P-value*	Non-submariner	Sub mariner	P-value*	Non-submariner	Sub mariner	P-value*	Non-submariner	Sub mariner	P-value*
Chronic health problems, N (%)												
0	96(53.3)	126(30.7)	<0.001	62(61.4)	56(44.8)	0.009	17(51.5)	52(27.8)	0.012	17(37.0)	18(18.4)	0.005
1	63(35.0)	152(37.1)		33(32.7)	47(37.6)		12(36.4)	75(40.1)		18(39.1)	30(30.6)	
≥2	21(11.7)	132(32.2)		6(5.9)	22(17.6)		4(12.1)	60(32.1)		11(23.9)	50(51.0)	
Cumulative Illness Rating Scale score, mean(SD)												
	1.66(1.16)	2.35(1.51)	<0.001	1.31(1.03)	1.70(1.23)	0.010	1.64(1.0)	2.33(1.43)	0.008	2.43(1.21)	3.23(1.59)	0.003

N: number, SD: standard deviation

* P-value was obtained by chi-square test or t-test

Table 3. Association of submarine service with the risk of multi-morbidity† and high disease burden‡

	Years of submarine service				
	0 year (N=180)	1-4 years (N=158)	5-9 years (N=107)	≥10 years (N=145)	P_{trend}¶
OR (95% CI)* for the association with multi-morbidity †					
Model 1	1	3.46(1.75-6.87)	2.59(1.37-4.89)	3.97(2.19-7.19)	<0.001
Model 2	1	3.97(1.91-8.25)	2.75(1.41-5.38)	3.78(2.06-6.94)	<0.001
OR (95% CI)* for the association with the high disease burden‡ estimated by Cumulative Illness Rating Scale					
Model 1	1	1.86(1.04-3.32)	2.36(1.37-4.05)	2.77(1.63-4.71)	0.001
Model 2	1	2.19(1.19-4.02)	2.78(1.58-4.89)	2.94(1.71-5.04)	0.001

OR (95% CI): odds ratio (95% confidence interval)

* estimated by multiple logistic regression analysis. In model 1, age was adjusted. In model 2, age, alcohol intake, smoking status (not included in the analysis for the disease burden), and job-ranking were adjusted.

† defined as two or more chronic health problems in a person

‡ defined as Cumulative Illness Rating Scale score ≥ 3 ¶ assessed by linear regression analysis, for which year of service was put in the model as a continuous variable.

Supplementary table 1. Relationship between submarine service year and multi-morbidiy and its burden
: A subgroup analysis in submariners

	Years of submarine service			
	1-4 years (N=158)	5-9 years (N=107)	≥10 years (N=145)	P_{trend} ¶
OR (95% CI)* for the association with multi-morbidity †				
Model 1	1	0.78(0.38,1.61)	1.23(0.52,2.91)	0.286
Model 2	1	0.60(0.28,1.27)	0.69(0.26,1.82)	0.865
OR (95% CI)* for the association with the high disease burden‡ estimated by Cumulative Illness Rating Scale				
Model 1	1	1.12(0.56,2.21)	1.21(0.52,2.80)	0.833
Model 2	1	0.89(0.44,1.83)	0.70(0.28,1.78)	0.272

OR (95% CI): odds ratio (95% confidence interval)

* estimated by multiple logistic regression analysis. In model 1, age was adjusted. In model 2, age, alcohol intake, smoking status (not included in the analysis for the disease burden), and job-ranking were adjusted.

† defined as two or more chronic health problems in a person

‡ defined as Cumulative Illness Rating Scale score ≥ 3 ¶ assessed by linear regression analysis, for which year of service was put in the model as a continuous variable.

Supplementary Table 2. Distribution of symptoms in each organ domain of Cumulative Illness Rating Scale

Organ domains	All Subjects			After excluding smokers and obese subjects		
	Non-submariner N(%)	Submariner N(%)	P-value*	Non-submariner N(%)	Submariner N(%)	P-value*
Overall	84(46.7)	284(69.3)	<0.001	13(17.6)	38(35.8)	0.007
Cardiac	2(1.1)	4(1.0)	0.880	0(0)	1(0.9)	1.000
Vascular	21(11.7)	125(30.5)	<0.001	6(8.1)	23(21.1)	0.023
Respiratory	74(41.1)	239(58.3)	<0.001	6(8.1)	16(14.7)	0.180
Eyes ear, nose, and throat	53(29.4)	85(20.7)	0.021	23(32.4)	21(19.3)	0.042
Upper gastrointestinal tract	5(2.8)	8(2.0)	0.529	3(4.1)	1(0.9)	0.182
Lower gastrointestinal tract	9(5.0)	12(2.9)	0.211	6(8.1)	5(4.6)	0.356
Musculoskeletal or tegumental	34(18.9)	96(23.4)	0.222	15(20.3)	22(20.2)	0.989
Neurological	5(2.8)	11(2.7)	0.948	1(1.4)	3(2.8)	0.648
Endocrine, metabolic, breast	63(35.0)	211(51.5)	<0.001	2(2.7)	11(10.1)	0.078
Other organ	4(2.2)	19(4.6)	0.163	3(4.1)	2(1.8)	0.395

N: number, SD: standard deviation

* P-value was obtained by chi-square test or Fisher's exact test

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract : **checked**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found : **checked**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported : **checked**
Objectives	3	State specific objectives, including any prespecified hypotheses : **checked**
Methods		
Study design	4	Present key elements of study design early in the paper : **checked**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection : **checked**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants : **checked**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable : **checked**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group : **checked**
Bias	9	Describe any efforts to address potential sources of bias : **checked**
Study size	10	Explain how the study size was arrived at : **checked**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why : **checked**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding : **checked**
		(*b*) Describe any methods used to examine subgroups and interactions : **checked**
		(*c*) Explain how missing data were addressed : **checked**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses : **checked**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed : **checked**
		(b) Give reasons for non-participation at each stage : **checked**
		(c) Consider use of a flow diagram : **checked**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders : **checked**
		(b) Indicate number of participants with missing data for each variable of interest : **checked**
Outcome data	15*	Report numbers of outcome events or summary measures : **checked**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included : **checked**
		(*b*) Report category boundaries when continuous variables were categorized :

		checked
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period : **Not applicable**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses : **checked**
Discussion		
Key results	18	Summarise key results with reference to study objectives : **checked**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias : **checked**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence : **checked**
Generalisability	21	Discuss the generalisability (external validity) of the study results : **checked**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based : **checked**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The association between submarine service and multi-morbidity: a cross-sectional study of Korean naval personnel

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Contributorship statements

Dr. Jihun Kang (first author) conceived of and designed the study; collected, analyzed, and interpreted the data; and wrote and revised the report. Prof. Yun-Mi Song (corresponding author) conceived of and designed the study; collected, analyzed, and interpreted the data; and provided important intellectual context and critical revisions for the report. Both authors have approved the final version for publication, and accept responsibility for the accuracy and integrity of the data and the analysis.

ABSTRACT

Objective: We aimed to estimate the prevalence of multi-morbidity (≥2 chronic health problems) among Korean submariners and to evaluate the association between submarine service, and multi-morbidity and disease burden.

Study Design and Setting: This cross-sectional study included 590 naval personnel who visited a Korean primary care clinic during 2014–2015. Data regarding general characteristics and morbidities were collected from medical records, and disease burden was assessed using the Cumulative Illness Rating Scale (CIRS). Multiple logistic regression analysis was used to evaluate the association between submarine service, and multi-morbidity and disease burden.

Results: The prevalence of multi-morbidity was 11.7% among 180 non-submariners and 32.2% among 410 submariners. The prevalence of multi-morbidity and the CIRS scores gradually increased with age. Submarine service was associated with higher risk of multi-morbidity and disease burden compared with non-submarine service even after adjusting for age, alcohol consumption, smoking status, and naval rank. However, a dose-response relationship was not evident between the duration of submarine service and the risk of multi-morbidity as well as high disease burden.

Conclusions: Submarine service was significantly associated with a higher risk of multi-morbidity and greater disease burden than non-submarine service. This finding suggests that multi-dimensional and holistic healthcare approaches are needed for submariners.

Keywords: Submarine, multi-morbidity, disease burden, occupational exposure

Strengths and limitations of this study

This is the first study to evaluate multi-morbidity as well as disease burden in submariners.

The cross-sectional design precludes any conclusions regarding the direction of causality in the relationship between submarine service and multi-morbidity.

The specificity of our study population, Korean submariners, limits the generalization of our findings to other populations.

INTRODUCTION

Multi-morbidity (the coexistence of ≥2 long-term diseases or medical conditions in one person) is associated with increased medical expenditure [1], decreased quality of life [2], and higher mortality [3]. With increasing life expectancy and an aging population [4], multi-morbidity has become an important public health issue [5] because elderly people are likely to have multiple coexisting medical conditions. Therefore, most multi-morbidity research has been performed among older populations [3 6], although multi-morbidity is not just an issue for elderly people [7]. A recent study found that >50% of people with multiple medical conditions were <65 years old [8], which indicates that multi-morbidity should be investigated in populations with a broader age range [9].

Military personnel are often relatively young people who undergo physical training and military drilling before deployment. Among military personnel, submariners are a unique population because they complete a specialized selection process and training to ensure that they can perform their demanding duties. Thus, submariners are considered a relatively healthy group at the time of their recruitment [10]. However, submariners are concurrently exposed to various environmental risk factors that can affect their health status, such as their confined work environment, physical inactivity, excessive caloric intake, circadian disruption, and isolation from family during deployment [11-13]. Few studies evaluating the effects of these occupational risk factors on submariners' health status have reported controversial findings. A Norwegian study revealed that submariners had increased risk of bladder cancer and non-melanoma skin cancer [14].

Similarly, a German study revealed that submariners had a higher rate of *Helicobacter pylori* infection compared to other naval personnel [15]. On the other hand, a British study revealed that submarine service was not associated with increased risk of mortality or specific diseases [16]. Moreover, little is known about whether submarine service is associated with multi-morbidity. Therefore, the present study aimed to estimate the prevalence of multi-morbidity among Korean submariners and to evaluate the association between submarine service, and multi-morbidity and disease burden by comparing submariners and non-submarine naval personnel.

METHODS AND MATERIALS

Study design and participants

This cross-sectional study analyzed data from the medical records of naval personnel who visited a primary care facility at the military base in Jinhae (Republic of Korea) between April 2014 and March 2015. Of the 1,004 men who visited the clinic, we excluded 332 men who had a temporary service commission (conscripted individuals who were not eligible for submarine service) and 82 men with missing information regarding their socio-demographic characteristics (N = 15) or disease status (N = 67). Thus, 590 permanently commissioned naval personnel who volunteered for professional naval service were ultimately included in the present study. We defined submariner as a person who had completed submarine training courses and worked in a submarine for ≥6 months, and categorized the subjects as either submariners (410 men) or non-submariners (180 men).

The study's protocol complied with the STROBE guidelines. In addition, the protocol was approved and the requirement for informed consent was waived by the institutional review board of the Armed Forces Medical Command in Seongnam, South Korea (AFMC-15088-IRB-15-068).

Data collection

The subjects' socio-demographic data (age, years of submarine service, and naval rank), anthropometric data (height and weight), and health behaviors (smoking status and alcohol consumption) were obtained by reviewing their medical records. Current smokers were defined as individuals who had smoked >100 cigarettes during their life and were currently smoking. Self-reporting was used to identify individuals who consumed alcohol. Body mass index (BMI, kg/m^2) was calculated as weight divided by height squared, and we defined obesity as a BMI of ≥25 kg/m^2, based on the definition for the Korean population [17].

We identified co-existing chronic health problems in several ways. First, using a self-administered questionnaire, we asked the study subjects to answer "yes" or "no" to each question regarding whether they had experienced or had received treatment for the chronic conditions: diabetes, chronic obstructive pulmonary disorder, asthma, hypertension, dyslipidemia, heart disease (congestive heart failure and ischemic heart disease), stroke, gastro-esophageal reflux, sleep apnea, arthritis, kidney disease, or psychological disorders. Next, an additional physician-led examination was carried out to identify any unreported conditions. In addition, we reviewed the medical records of each study subject. We reviewed medical records from the date of implementation of the electronic medical record system (2013) onwards and data was extracted and medical conditions classified using disease codes from the 10th revision of the International Statistical Classification of Diseases and Health Problems (ICD-10). The presence of multi-morbidity (≥2 chronic medical conditions) was evaluated by counting the number of chronic health conditions that each subject had.

We estimated disease burdens based on the illnesses and their severities using the Cumulative Illness Rating Scale (CIRS) [18]. This tool assesses symptoms in 14 organ domains (cardiac; vascular; hematological; respiratory; eye, ear, nose, and throat; upper gastrointestinal tract; lower gastrointestinal tract; hepatic and pancreatic; renal; genitourinary; musculoskeletal and tegumental; neurological; endocrine, metabolic, breast; and psychiatric). The CIRS was originally developed by Linn et al. [19] to assess chronic medical problems in a comprehensive manner, and was subsequently revised by Miller et al. [20] to measure common morbidities among elderly patients. This tool was later modified by Hudon et al. [18] to estimate multi-morbidity in the primary care setting, and was found to be a reliable and valid tool [2 21 22]. The CIRS score for each organ system ranges from 0 (no problems affecting that system) to 4 (extremely severe problems), and the total CIRS score is calculated by adding the scores for all 14 organ domains (range: 0–56). If a person currently smokes or has a high BMI (≥25 kg/m^2), then the person is considered to have disease burden in the respiratory and metabolic systems, respectively. The total CIRS score has a left-skewed distribution because it is very rare for a person to have severe medical conditions in every organ system.

Statistical analysis

The demographic characteristics, distributions of chronic health problems, and CIRS scores were compared between submariners and non-submariners using the chi-square test and t-test, as appropriate. We also compared the distributions of chronic health problems and CIRS scores for three age strata (<30 years, 30–39 years, and ≥40 years) because the age distributions were significantly different between the submariners and non-submariners. There is no standardized cut-off value for high disease burden based on CIRS score, and we arbitrarily defined subjects in the upper tertile of CIRS scores (≥3) as having high disease burden. We also evaluated the associations of submarine service with multi-morbidity and high disease burden using multiple logistic regression analysis after adjusting for age, alcohol consumption, smoking status, and naval rank (reference group: non-submariners with 0 years of submarine service). However, we did not include smoking status as a covariate in the model for disease burden, because it is a component of the CIRS score. All statistical analyses were performed using PASW Statistics software (version 21.0; SPSS Inc., Chicago, IL, USA). Two-tailed *P*-values of <0.05 were considered significant.

RESULTS

Table 1 shows the subjects' characteristics. Compared to non-submariners, submariners were significantly older, were more likely to be current smokers and obese, and had a higher naval rank ($p < 0.05$). Table 2 shows the distributions of chronic health problems and CIRS scores among all subjects and in the three age strata. The prevalence of multi-morbidity was 11.7% among non-submariners and 32.2% among submariners. The prevalence of multi-morbidity and the CIRS scores gradually increased with age among both submariners and non-submariners. The number of chronic health problems and CIRS scores were significantly higher among submariners than non-submariners, across all age groups.

Table 3 shows the adjusted associations of submarine service with risks of multi-morbidity and high disease burden (CIRS of ≥3). Submarine service of one year or longer was positively associated with multi-morbidity and disease burden as compared with less than one-year of submarine service. This association remained significant after adjusting for age, alcohol consumption, smoking status, and naval rank. However, a dose-response relationship according to duration of submarine service was not evident (Supplementary Table 1).

Supplementary Table 2 shows the prevalence of symptoms in each CIRS organ domain. Compared to non-submariners, submariners more frequently experienced symptoms in the vascular, respiratory, ear/nose/throat, and endocrine domains. Both groups had similar prevalences of symptoms in the cardiac, upper and lower gastrointestinal, musculoskeletal or tegumental, and neurological domains. When we excluded current smokers and obese subjects from the CIRS domain analyses, no significant difference was observed in the endocrine and respiratory domain.

DISCUSSION

The present study is the first to examine the prevalence of multi-morbidity and disease burden among submariners. Use of the CIRS score allowed us to provide more comprehensive data, especially regarding the disease burden, compared to previous studies [3 8 23]. Based on our findings, approximately 30% of submariners had multi-morbidity, and this rate was approximately 3 times greater than the prevalence among non-submariner naval personnel (11.7%). The higher rate of multi-morbidity among submariners was consistently observed in different age strata, which suggests that the significant difference in the multi-morbidity rate was not caused by different age distributions.

A previous study in primary care setting has shown that prevalence of multi-morbidity might be comparable between studies when multi-morbidity is defined as ≥2 disease entities, regardless of the specific disease entity definitions in each study [24]. The prevalence of multi-morbidity varies according to study. After excluding elderly subjects (to simplify the age-based comparisons), we found that the prevalence of multi-morbidity among non-submariners was 11.7%, which was lower than the reported prevalence in the Netherlands (24.2% among 20–59-year-old men from the general population) [23], Scotland (20.5% among 25–65-year-old men from the general population) [8], and Canada (20.4% among 18–64-year-old men from the general population) [25]. However, the difference in the prevalence of multi-morbidity across studies might have been a result of the varying definitions and methods for assessing multi-morbidity, as well as the study settings.

In the present study, submariners more frequently experienced symptoms in the vascular, respiratory, endocrine, and ear/nose/throat CIRS domains than non-submariners (Supplementary Table 2). This finding is partially consistent with the findings of a previous study, which revealed that respiratory infections and elevated blood pressure without a hypertension diagnosis were common morbidities among American submariners [26]. We assume that our findings may be related to the fact that current smoking and obesity are counted as respiratory and endocrine diseases, respectively, in the CIRS system [18]. Although the smoking rate was lower in submariners than in non-submariners, worse air quality from the enclosed space of a submarine might have contributed to the more prevalent respiratory and ear/nose/throat symptoms.

We observed positive associations between age and multi-morbidity among both non-submariners and submariners, and this association has been clearly documented in previous studies [6 8 23]. In addition, our finding of increasing disease burden (estimated using CIRS) with age was similar to the findings from a Canadian study [21]. However, submariners had a greater prevalence of multi-morbidity and greater disease burden in all age groups, compared to non-submariners. Although the current smoking rate among submariners was comparable to that among the general population of Korean men (47% in 2012) [27], the higher smoking rate among submariners may explain their greater disease burden, as current smoking is considered a respiratory problem in the CIRS system. In addition, the submariners' obesity rate was higher than that among Korean non-submariners, American small submarine crews (17.9% in 2011) [28], and American police officers and firefighters (30.7% in 2002) [29], which may also explain the difference in disease burden. Although different cut-off values for obesity are used for Korean and American populations (≥25 kg/m^2 vs. ≥30 kg/m^2), we think the results are comparable in terms of obesity diagnoses because Asian populations have a higher body fat composition for any given BMI than Caucasian populations [30] and increased all-cause mortality is associated with BMI of ≥25 kg/m^2 in the Korean population [31].

Unfortunately, the confined submarine environment is not conducive to vigorous activity and exercise during deployment [32], and submariners' caloric intake tends to exceed their expenditure during this time [12]. Moreover, submariners' shift work schedules during their deployment may increase their risk of metabolic syndrome [33]. Thus, the combination of low physical activity levels, excessive caloric intake, and circadian misalignment may elevate the risk of accumulating abdominal and visceral fat [34], which could explain the prevalence of obesity among submariners. These factors may also have contributed to the high disease burden and prevalence of multi-morbidity among submariners, compared to non-submariners.

As age is strongly associated with multi-morbidity [8 23], it is possible that the association between multi-morbidity and service years was confounded by age. However, after adjusting for age, the positive associations of submarine service with multi-morbidity as well as disease burden were only slightly attenuated. Thus, our findings negate a significant confounding effect of age on the association.

Submariners are exposed to several health risk factors, such as *Helicobacter pylori* infection, that are related to overcrowding and extremely limited sanitary facilities [15], increased cortisol levels related to chronic stress state and sleep deprivation [35], and low air quality in an enclosed space [36]. These risk factors may have cumulative negative effects on submariners' health status, which might partially explain the higher prevalence of multi-morbidity in this population. Nevertheless, previous studies have reported conflicting findings regarding the health of submariners. For example, a study by the American Navy revealed that submarine duty did not increase the risk of hospitalization for 16 major diagnostic categories and submarine-associated diagnoses [37]. However, we could not directly compare the findings of that study and our study, as we used different methods to identify morbidities (outpatient clinical records vs. hospitalization records and multi-morbidity vs. single disease entities).

Few studies have evaluated the risk of mortality among submariners, and those studies have reported no significant association. A British study of Royal Navy submarine crews concluded that working in a submarine was not associated with increased cancer mortality, although the authors detected an increase in liver cirrhosis-related mortality that might not be attributable to the submarine environment [16]. A Norwegian study also failed to detect differences in all-cause mortality among surface vessel and submarine crews, and the submariners had a lower rate of all-cause mortality than the general population of Norwegian men [14]. Several explanations were proposed for the null finding from the Norwegian study. First, the participants had relatively low mean service times (2.7 years), which may have been insufficient to noticeably affect the subjects' mortality. Another plausible explanation is that morbidity may not significantly affect mortality in a relatively young and healthy population, unlike older populations [3]. Furthermore, the "healthy soldier effect" may result in submariners having a good initial health state, as military personnel and submariners are specially selected to perform challenging tasks, which could diminish the adverse effects of the submarine working environment [10].

There are several limitations to the present study. First, the cross-sectional design precludes any conclusions regarding the causality of the relationship between submarine service and risk of multi-morbidity. However, it seems logical to assume that submarine work increases multi-morbidity, rather than vice versa, because it is very unlikely that multi-morbidity would drive an individual to submarine work. Second, the absence of a standardized definition led us to create our own arbitrary definition for multi-morbidity (≥2 coexisting chronic conditions in a single patient), and it is possible that we underestimated or overestimated the prevalence of multi-morbidity. Third, selection bias is possible, as it was not possible to blind the physicians to each subject's status as a submariner or non-submariner. In addition, subjects who visited the clinic may have had relatively poor health status, compared to other naval personnel who did not seek medical attention. Fourth, the specificity of our study population (Korean submariners) and the absence of an age-matched non-navy personnel control group, may limit the generalization of our findings to other populations.

In conclusion, this Korean study revealed that, compared to non-submarine service, submarine service was significantly associated with a higher risk of multi-morbidity and greater disease burden, even after adjusting for relevant covariates. These findings suggest that scrupulous attention is needed to assess submariners and manage their health conditions in multi-dimensional and holistic ways. Further research is needed to examine the effects of multi-morbidity on disease patterns, quality of life, and overall mortality among submariners.

Conflicts of interest: None.

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Data Sharing Statement: Access to the dataset used in this study is restricted by Ministry of National Defense, Republic of Korea.

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Table 1. General and clinical characteristics of study subjects

	Overall (N=590)	Non-submariner (N=180)	Submariner (N=410)	*P*-value*
Age, years, mean (SD)	33.2(8.5)	31.2(9.9)	34.1(7.7)	<0.001
Height, cm	173.8(0.1)	173.4(0.1)	174.0(0.1)	0.189
Body mass index, kg/m^2, mean (SD)	25.0(3.0)	24.3(3.0)	25.3(2.9)	<0.001
≥25 kg/m^2, N(%)	267(45.3)	63(35.0)	204(49.8)	0.001
18.5-24.9 kg/m^2, N(%)	322(54.6)	116(64.4)	206(50.2)	
<18.5 kg/m^2, N(%)	1(0.2)	1(0.6)	0(0)	
Alcohol consumption, N(%)	487(82.5)	152(84.4)	335(81.7)	0.420
Current smoker, N(%)	277(46.9)	68(37.8)	209(51.0)	0.003
Job-Ranking, N(%)				<0001
Officer	103(17.5)	31(17.2)	72(17.6)	
Petty officer	465(78.8)	127(70.6)	338(82.4)	
Navy civilian	22(3.7)	22(12.2)	0(0%)	
Mean (SD) years of service in submarine	NA	0	7.1(5.3)	NA

N: number of subjects, SD: standard deviation, NA: not applicable

* *P*-value was obtained from the t-test for continuous variables and chi-square test for categorical variables

Table 2. Comparison of the number of chronic health problems and mean Cumulative Illness Rating Scale (CIRS) score between submariners and non-submariners by age group

	Overall			<30 years			30-39 years			≥40 years		
	Non-submariner	Sub mariner	*P*-value*	Non-submariner	Sub mariner	*P*-value*	Non-submariner	Sub mariner	*P*-value*	Non-submariner	Sub mariner	*P*-value*
Chronic health problems, N (%)												
0	96(53.3)	126(30.7)	<0.001	62(61.4)	56(44.8)	0.009	17(51.5)	52(27.8)	0.012	17(37.0)	18(18.4)	0.005
1	63(35.0)	152(37.1)		33(32.7)	47(37.6)		12(36.4)	75(40.1)		18(39.1)	30(30.6)	
≥2	21(11.7)	132(32.2)		6(5.9)	22(17.6)		4(12.1)	60(32.1)		11(23.9)	50(51.0)	
Cumulative Illness Rating Scale score, mean (SD)												
	1.66(1.16)	2.35(1.51)	<0.001	1.31(1.03)	1.70(1.23)	0.010	1.64(1.0)	2.33(1.43)	0.008	2.43(1.21)	3.23(1.59)	0.003

N: number, SD: standard deviation

* *P*-value was obtained from the chi-square test or t-test

Table 3. Association of submarine service with the risk of multi-morbidity† and high disease burden‡

	Years of submarine service				
	0 year (N=180)	1-4 years (N=158)	5-9 years (N=107)	≥10 years (N=145)	P_{trend}¶
OR (95% CI)* for the association with multi-morbidity †					
Model 1	1	3.46(1.75-6.87)	2.59(1.37-4.89)	3.97(2.19-7.19)	<0.001
Model 2	1	3.97(1.91-8.25)	2.75(1.41-5.38)	3.78(2.06-6.94)	<0.001
OR (95% CI)* for the association with the high disease burden‡ estimated by Cumulative Illness Rating Scale					
Model 1	1	1.86(1.04-3.32)	2.36(1.37-4.05)	2.77(1.63-4.71)	0.001
Model 2	1	2.19(1.19-4.02)	2.78(1.58-4.89)	2.94(1.71-5.04)	0.001

OR (95% CI): odds ratio (95% confidence interval)

* estimated by multiple logistic regression analysis. In model 1, age was adjusted. In model 2, age, alcohol intake, smoking status (not included in the analysis for the disease burden), and job-ranking were adjusted.

† defined as two or more chronic health problems in a person

‡ defined as Cumulative Illness Rating Scale (CIRS) score ≥ 3 ¶ assessed by linear regression analysis, with years of service as a continuous variable.

Supplementary table 1. Relationship between submarine service year and multi-morbidiy and its burden
: A subgroup analysis in submariners

	Years of submarine service			
	1-4 years (N=158)	5-9 years (N=107)	≥10 years (N=145)	P_{trend} [¶]
OR (95% CI)* for the association with multi-morbidity †				
Model 1	1	0.78(0.38,1.61)	1.23(0.52,2.91)	0.286
Model 2	1	0.60(0.28,1.27)	0.69(0.26,1.82)	0.865
OR (95% CI)* for the association with the high disease burden‡ estimated by Cumulative Illness Rating Scale				
Model 1	1	1.12(0.56,2.21)	1.21(0.52,2.80)	0.833
Model 2	1	0.89(0.44,1.83)	0.70(0.28,1.78)	0.272

OR (95% CI): odds ratio (95% confidence interval)

* estimated by multiple logistic regression analysis. In model 1, age was adjusted. In model 2, age, alcohol intake, smoking status (not included in the analysis for the disease burden), and job-ranking were adjusted.

† defined as two or more chronic health problems in a person

‡ defined as Cumulative Illness Rating Scale score ≥ 3 ¶ assessed by linear regression analysis, for which year of service was put in the model as a continuous variable.

Supplementary Table 2. Distribution of symptoms in each organ domain of Cumulative Illness Rating Scale

Organ domains	All Subjects			After excluding smokers and obese subjects		
	Non-submariner N(%)	Submariner N(%)	P-value*	Non-submariner N(%)	Submariner N(%)	P-value*
Overall	84(46.7)	284(69.3)	<0.001	13(17.6)	38(35.8)	0.007
Cardiac	2(1.1)	4(1.0)	0.880	0(0)	1(0.9)	1.000
Vascular	21(11.7)	125(30.5)	<0.001	6(8.1)	23(21.1)	0.023
Respiratory	74(41.1)	239(58.3)	<0.001	6(8.1)	16(14.7)	0.180
Eyes ear, nose, and throat	53(29.4)	85(20.7)	0.021	23(32.4)	21(19.3)	0.042
Upper gastrointestinal tract	5(2.8)	8(2.0)	0.529	3(4.1)	1(0.9)	0.182
Lower gastrointestinal tract	9(5.0)	12(2.9)	0.211	6(8.1)	5(4.6)	0.356
Musculoskeletal or tegumental	34(18.9)	96(23.4)	0.222	15(20.3)	22(20.2)	0.989
Neurological	5(2.8)	11(2.7)	0.948	1(1.4)	3(2.8)	0.648
Endocrine, metabolic, breast	63(35.0)	211(51.5)	<0.001	2(2.7)	11(10.1)	0.078
Other organ	4(2.2)	19(4.6)	0.163	3(4.1)	2(1.8)	0.395

N: number, SD: standard deviation

* P-value was obtained by chi-square test or Fisher's exact test

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract : **checked, page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found : **checked, page 3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported : **checked, page 5-6**
Objectives	3	State specific objectives, including any prespecified hypotheses : **checked, page 6**
Methods		
Study design	4	Present key elements of study design early in the paper : **checked, Page 6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection : **checked, Page 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants : **checked, Page 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable : **checked, page 7-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group : **checked, page 7-8**
Bias	9	Describe any efforts to address potential sources of bias : **checked, page 15**
Study size	10	Explain how the study size was arrived at : **N/A**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why : **checked, page 9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding : **checked, page 9**
		(*b*) Describe any methods used to examine subgroups and interactions : **checked, page 9**
		(*c*) Explain how missing data were addressed : **checked, page 6**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy, **N/A**
		(*e*) Describe any sensitivity analyses : **checked, page 10**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed : **Page 6**
		(b) Give reasons for non-participation at each stage : **checked, page 6**
		(c) Consider use of a flow diagram : **N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders : **checked, page 10**
		(b) Indicate number of participants with missing data for each variable of interest : **checked, Page 6**
Outcome data	15*	Report numbers of outcome events or summary measures : **checked, page 10**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included : **checked, page 9-10**
		(*b*) Report category boundaries when continuous variables were categorized : **checked, page 8**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period : **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses : **checked, page 10**
Discussion		
Key results	18	Summarise key results with reference to study objectives : **checked, page 11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias : **checked, page 15**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence : **checked, page 13-15**
Generalisability	21	Discuss the generalisability (external validity) of the study results : **checked, page15**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based : **checked, page 16**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.