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Association between serum high-density lipoprotein cholesterol and lung function in adults: three cross-sectional studies from US and Korea National Health and Nutrition Examination Survey

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ABSTRACT

Introduction Cholesterol is an irreplaceable nutrient in pulmonary metabolism; however, studies on high-density lipoprotein cholesterol (HDL-C) levels have shown conflicting results regarding lung function. Therefore, we investigated the association between lung function and HDL-C levels in three cross-sectional studies conducted in the USA and South Korea.

Methods US National Health and Nutrition Examination Survey (NHANES) III, US NHANES 2007–2012, and Korea National Health and Nutrition Examination Survey (KNHANES) IV–VII performed spirometry and met the American Thoracic Society recommendations. Multiple linear regression models were used to determine the relationship between serum lipid levels and lung function. The models were adjusted for age, sex, household income, body mass index, smoking pack year, use of lipid-lowering medication and race. Serum HDL-C levels were classified into three groups to assess the dose–response relationship according to the guideline from the National Cholesterol Education Program-Adult Treatment Panel III.

Results The adult participants of the KNHANES (n=31 288), NHANES III (n=12 182) and NHANES 2007–2012 (n=9122) were analysed. Multivariate linear regression analysis of the serum cholesterol profiles revealed that only serum HDL-C was associated with forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) in all three studies. A 1 SD increase in the HDL-C level increased the percent predicted FVC by 0.5%–1.5% p, and the per cent predicted FEV_1 by 0.5%–1.7% p. In terms of HDL-C levels, correlations between the HDL-C groups and the per cent predicted FVC and FEV_1 showed dose–response relationships. Compared with the normal group, high HDL-C levels increased FVC by 0.75%–1.79% p and FEV_1 by 0.55%–1.90% p, while low levels led to 0.74%–2.19% p and 0.86%–2.68% p reductions in FVC and FEV_1, respectively. Subgroup analyses revealed weaker associations in females from KNHANES and NHANES III.

Conclusion In the three nationwide cross-sectional studies, high HDL-C levels were associated with improved FVC and FEV_1. However, future studies are needed to confirm this correlation and elucidate the underlying mechanisms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies on the relationship between high-density lipoprotein (HDL) cholesterol and lung function showed conflicting results; HDL-cholesterol was inversely correlated with lung function in a study with Korean adolescents, and was positively correlated with forced expiratory volume in 1 s (FEV_1) in a study with US National Health and Nutrition Examination Survey III data.

WHAT THIS STUDY ADDS

⇒ This study strengthens evidence that HDL-cholesterol may be associated with increased forced vital capacity and FEV_1.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The role of cholesterol metabolism in normal physiology and pathology of lung needs further investigation.

INTRODUCTION

Cholesterol is an irreplaceable nutrient in pulmonary metabolism.[1–4] As the major neutral lipid in pulmonary surfactant, an increased amount of cholesterol compromises surface tension, thereby increasing mechanical stress-induced lung injury.[5] Moreover, animal models genetically deficient in high-density lipoprotein (HDL) show abnormalities in lung development and physiology.[6 7] However, little is known regarding the clinical significance of circulating lipoproteins and cholesterol metabolites in lung function.

Reduced low-density lipoprotein cholesterol (LDL-C) may suppress inflammation and reduce lung function decline in patients with chronic obstructive pulmonary disease (COPD).[8] However, studies on

HDL-cholesterol (HDL-C) have shown conflicting results regarding lung function.[3 9–11] As the relationship between serum cholesterol levels and pulmonary function remains unclear, we used three independent national surveys conducted in the USA and South Korea to examine the association between serum cholesterol levels and pulmonary function.

METHODS

Study design and population

We included datasets from the 2007–2012 US National Health and Nutrition Examination Survey (NHANES), 1988–1994 US NHANES III, and 2007–2018 Korea NHANES (KNHANES) IV–VII. Each of the three surveys is an independent, nationally representative, cross-sectional studies with a large sample size. Information on the design and protocols of the NHANES 2007–2012 and NHANES III can be found on the National Center for Health Statistics website.[12–16] Additionally, details of the KNHANES study design have been described by the Korea Centers for Disease Control and Prevention.[17 18] For our study, participants were limited to healthy adults aged≥17 years. Of the KNHANES participants, however, only adults aged≥40 years were eligible for inclusion in our study, because spirometry was performed exclusively for that age group. To adjust this possible bias, we performed sensitivity analysis by subgroup analysis for adults aged≥40 years in the US surveys.

To address our hypotheses, we excluded participants if any critical variables necessary for analysis were insufficient (figure 1). Specifically, we excluded those with missing or zero survey weights, incomplete or unreliable spirometry results (in accordance with the American Thoracic Society (ATS) guidelines), and lack of data on anthropometric measures, smoking history and cholesterol measurements. In addition, we excluded individuals with medical history of asthma, COPD or malignant tumours to account for the possibility of reverse causality, where such conditions may affect lung function and cholesterol levels.

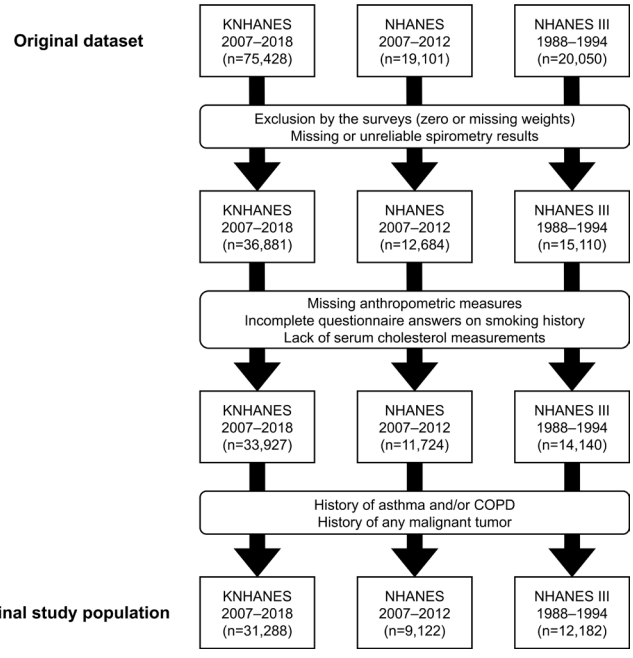

Figure 1 Flow chart of the study population. Exclusion criteria and resulting numbers of participants in the surveys are shown. COPD, chronic obstructive pulmonary disease; (K)NHANES, (Korea) National Health and Nutrition Examination Survey.

Patient and public involvement

This study was independent from the public in terms of the design, conduct, reporting or dissemination plans of our research. All datasets used in this study are deidentified and publicly available.

Survey assessments

In all the surveys, trained interviewers collected data on age, sex, race, ethnicity, household income, medical history and smoking history. We categorised race/ethnicity into non-Hispanic white (Caucasian), non-Hispanic black (Black), Hispanic (Mexican American and other Hispanics) and others (including Asians). In the KNHANES, all participants were considered Asians because of the monoethnic nature of the sample population. Disease and medication statuses were determined based on participants' responses to the survey questionnaire.

Spirometry

In all the surveys, weight (kg), height (cm) and spirometry results were obtained at mobile examination centres. Participants were excluded from spirometry testing if they experienced chest pain or had a recent eye, chest or abdominal surgery. The reliability and reproducibility of the spirometry results were assessed according to the standards of ATS and the European Respiratory Society.[19]

In US surveys, each qualified participant performed five trials in NHANES III and three in NHANES 2007–2012. The NHANES 2007–2012 studies used the same spirometers (Ohio 822/827 dry rolling-seal volume spirometers) as the NHANES III studies. In KNHANES, each participant performed at least three trials until at least two acceptable sets of flow-volume curves were obtained. KNHANES IV–VI (2007–2015) used the Vmax 2130 dry rolling-seal spirometer (SensorMedics Corporation, Yorba Linda, California), and KNHANES VII (2016–2018) used the Vyntus Spiro portable spirometer (Vyaire Medical GmbH, Hoechberg, Germany).[20] In contrast to the US surveys, bronchodilators were not used in KNHANES; therefore, postbronchodilator data were not included in this study.

To address racial differences in lung function and facilitate comparisons between both countries, predicted forced expiratory volume in 1 s (FEV_1) and forced vital

capacity (FVC) were estimated using the Global Lung Function Initiative 2012 equations.[21 22] Additionally, considering that each nation has its reference equation, we employed a sensitivity analysis using predicted lung function values calculated from the NHANES III and Korean reference equations.[23 24]

Cholesterol measurements

In NHANES 2007–2012 and NHANES III, serum total cholesterol, and HDL-C levels were measured at mobile examination centres, regardless of the fasting status of participants. Both were assayed using a Hitachi 704 Analyzer in NHANES III and a Roche Modular P chemistry analyzer in 2007–2012 NHANES. LDL-C levels were calculated using the Friedewald equation.[25] This equation only applied to examinees who fasted ≥9 hours before blood collection and those with ≤400 mg/dL triglyceride. Apolipoprotein A-I was only measured in phase I of NHANES III (1988–1991), thereby its matching strata, sampling units and weight were employed for analysis. Details on the measurement method are discussed elsewhere.[9]

Similarly, in KNHANES, serum total cholesterol and HDL-C levels were measured at mobile examination centres using a Hitachi Automatic Analyzer 7600/7600-210 (Hitachi, Tokyo, Japan), and LDL-C levels were calculated using the Friedewald equation. Notably, KNHANES has participated in the US Centers for Disease Control and Prevention (CDC) Lipid Standardization Program, and all HDL-C measurements were calibrated to US CDC standards.[26]

To analyse LDL-C levels, fasting subsample weights were used in NHANES III and NHANES 2007–2012 to adjust for the exclusion of a considerable number of participants. Conversely, in KNHANES, fasting subsample weights were not provided; however, 97.0% of participants included in our study fasted for at least 9 hours.

Statistical analyses

T-tests with Taylor series variance estimation method were used to compare HDL-C between subgroups. Multivariate linear regression models, also using the Taylor series method, were employed for each lipid component (total cholesterol, HDL-C and LDL-C). These models were adjusted for age, sex, household income, body mass index (BMI), BMI squared, smoking pack year, use of antilipemics and race. The percentages of predicted FEV_1 and FVC and FEV_1/FVC were analysed as dependent variables. In KNHANES, all models were adjusted for the same factors except race, given the monoethnic nature of the sample population.

Furthermore, participants were categorised into three groups based on their serum HDL-C levels to assess the dose–response relationship according to the classification criteria from the Adult Treatment Panel III (ATP III) guideline.[27] The 'low-HDL-C' group included subjects with HDL-C levels<40 mg/dL, while an HDL-C level≥60 mg/dL was considered 'high'. The 'normal' group was chosen as the reference for the multiple regression models. Sensitivity analyses were conducted by applying different cut-offs for categorising: (1) specific thresholds for the 'low' groups to account for sex differences in HDL-C levels (eg, 40 mg/dL for males and 50 mg/dL for females, following the definition criteria of metabolic syndrome), and (2) categorising into five groups using 5th, 35th, 65th and 95th percentiles calculated within each sex in each dataset.

All analyses were performed using SAS V.9.4 (SAS Institute). The 'SURVEYFREQ', 'SURVEYMEANS' and 'SURVEYREG' procedures were used to reflect complex survey designs with stratification, clustering and weighting in the analyses. P values less than 0.05 were considered significant for our analyses.

RESULTS

Population characteristics

The weighted mean ages of the participants included in KNHANES, NHANES III and NHANES 2007–2012 were 52.0, 41.3 and 42.5, respectively (table 1). Korean participants were prominently older than US participants because spirometry was performed only in adults aged ≥40 years. Additionally, sex was evenly distributed in US NHANES; however, there were 43.3% males in KNHANES. BMI was lowest in the KNHANES and highest in NHANES 2007–2012. Furthermore, cigarette smoking was most prevalent in NHANES III; current and ex-smokers accounted for 25.2% and 21.8% of the population, respectively. Lastly, the racial distribution of the US surveys changed over time; Asians and other mixed races increased from 1.4% to 9.2%, and the Blacks decreased from 26.9% to 20.2%.

HDL-C is associated with an increase in FVC and FEV_1

We investigated the association between the levels of the different types of cholesterol and lung function in the three cross-sectional studies by conducting multivariate linear regression analyses using the Taylor series method for sampling error estimation (figure 2 and online supplemental table S1 in the Supporting Information). HDL-C showed a consistent association with the per cent predicted FVC and FEV_1; a 1 SD increase in the serum HDL-C level increased FVC and FEV_1 by 0.5%–1.7% p ($p<0.0001$). In contrast, serum total cholesterol or LDL-C level showed no consistent correlation with the lung function markers FVC and FEV_1. Lastly, the association between FEV_1/FVC and all the cholesterol markers was not significant or consistent across the three surveys.

To evaluate the potential interaction effects among subgroups in the three surveys, subgroup analyses were conducted based on age, sex and use of antilipemic medicine. Male subjects had lower serum HDL-C levels than females by 6.0 to 10.8 mg/dL in all three surveys (online supplemental table S2 in the supporting information). The young group, defined as those less than 40

Table 1 General characteristics of the study population

Variables	KNHANES IV-VII 2007–2018 (n=31 288)	US NHANES III 1988–1994 (n=12 182)	US NHANES 2007–2012 (n=9122)
Age, mean (SD)	52.0 (13.6)	41.3 (16.7)	42.5 (15.3)
Male sex, N (%)	13 544 (43.3)	5932 (48.7)	4648 (50.7)
BMI, kg/m^2, mean (SD)	24.3 (3.2)	26.2 (5.4)	28.3 (6.3)
Pulmonary function indexes, %, mean (SD)			
FVC, % predicted	101.2 (12.7)	100.0 (12.9)	101.0 (12.7)
FEV_1, % predicted	98.5 (13.5)	97.2 (13.8)	97.9 (13.2)
FEV_1/FVC	78.7 (7.1)	79.6 (8.0)	79.2 (7.3)
Serum cholesterol measurements, mg/dL, mean (SD)			
Total cholesterol	193.0 (36.8)	200.6 (42.7)	195.8 (40.5)
HDL-cholesterol	48.9 (11.8)	50.6 (15.1)	52.7 (15.6)
LDL-cholesterol*	117.2 (32.4)	125.1 (37.1)	115.2 (34.2)
Use of antilipidemic medicine, N (%)	3123 (10.0)	314 (2.6)	1170 (12.8)
Smoking pack year, mean (SD)	8.5 (15.0)	10.6 (20.2)	3.0 (10.7)
Smoking status			
Current smoker, N (%)	5308 (17.0)	3071 (25.2)	1821 (19.7)
Former smoker, N (%)	6713 (21.5)	2657 (21.8)	1671 (19.7)
Race, N (%)			
Asian or others†	31 288 (100)	174 (1.4)	840 (9.2)
Black		3271 (26.9)	1846 (20.2)
Hispanic		3992 (32.8)	2780 (30.5)
Caucasian		4745 (39.0)	3656 (40.1)

Characteristics are weighted to represent the mean national populations in every survey.
*The numbers of included subjects for LDL-cholesterol were n=30 061 (KNHANES), 5358 (NHANES III), and 4084 (NHANES 2007–2012).
†Race is assumed 100% Asian in KNHANES owing to the monoethnic nature of the Republic of Korea.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL, high-density lipoprotein; (K)NHANES, (Korea) National Health and Nutrition Examination Survey; LDL, low-density lipoprotein.;

years old, and the lipid-lowering agent user group had 2.5 and 2.1 mg/dL lower serum HDL-C levels compared with their counterparts in NHANES 2007–2012, but there were no differences in other two surveys.

The association between serum HDL-C level and the percent predicted FVC was consistent across all subgroups in each survey, except for antilipemic users in KNHANES (figure 3). Although there was a loss of association in the antilipemic users from KNHANES, it was noteworthy that the interaction effects of antilipemic use were not significant; thus, this loss of association might result from chance due to multiple comparisons or decreased statistical power in subgroups. Sex differences were observed in the relationship between serum HDL-C level and FVC in KNHANES and NHANES III; females exhibited lower beta coefficients, indicating a weaker association, in these two surveys. This consistent correlation between serum HDL-C level and lung function was also evident in the subgroup analyses in the association with FEV_1. Women showed a weaker association between serum HDL-C level and FEV_1 than men in KNHANES (online supplemental figure S1 in the supporting information). The loss of association in antilipemic users was more pronounced in the relationship between serum HDL-C level and FEV_1 across all three surveys. However, no significant heterogeneity was detected (P for interaction>0.05).

Lastly, we assessed the dose–response relationship between HDL-C and lung function markers by categorising the participants into normal (reference), low-HDL-C, and high-HDL-C groups according to the ATP III guideline.[27] The association between the HDL-C groups and the per cent predicted FVC and FEV_1 was consistent with a dose–response relationship in all three surveys (figure 4); the high-HDL-C group showed an increase in the predicted percentages for FVC and FEV_1, and the low-HDL-C group showed the opposite trend.

In summary, we observed a positive linear relationship between the per cent predicted FVC and FEV_1, and serum HDL-C level across the three nationwide surveys.

Sensitivity analyses

To ensure the robustness and validity of our findings, we conducted various sensitivity analyses.

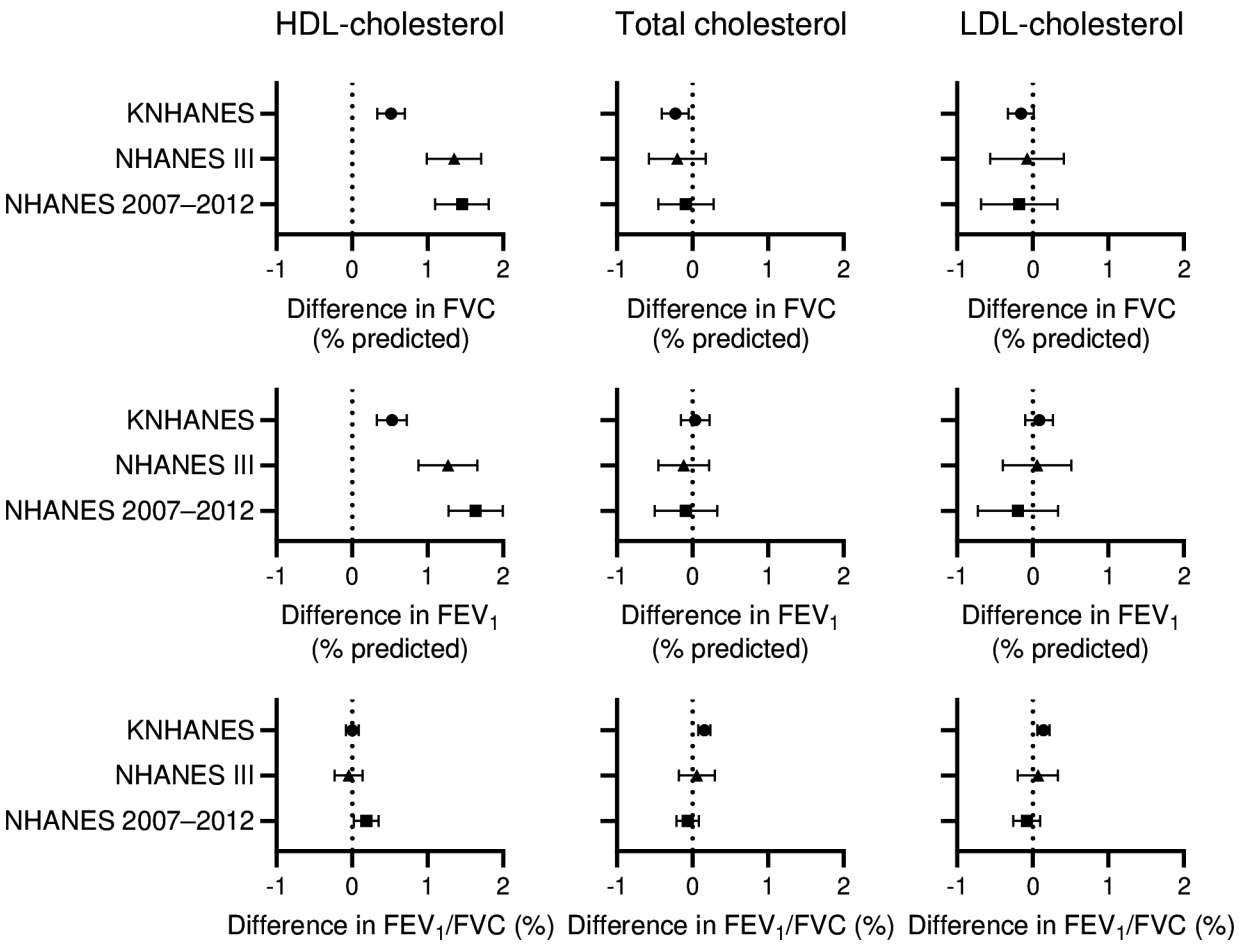

Figure 2 Association between serum lipid profiles and lung function. The graph illustrates predicted differences in the per cent predicted FVC, FEV_1 and the FEV_1/FVC ratio associated with an increase in serum lipid variables: (Left) HDL-cholesterol, (Center) Total cholesterol, and (Right) LDL-cholesterol. Results from each survey are distinguished using unique symbols. Beta coefficients with their 95% CIs are presented for each cholesterol variables, calculated per 1-SD shifts. The linear regression models were adjusted for the following covariates: age, sex, household income in quartiles, body mass index (BMI), BMI^2, use of antilipidemic medicine, smoking pack year and race (Black, Hispanic, White vs Asian or others). The numbers of included subjects for LDL-cholesterol were 30 061 (KNHANES), 5358 (NHANES III) and 4084 (NHANES 2007–2012). Detailed numerical data corresponding to these graphical representations can be found in online supplemental table S1 in the supporting information. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; (K)NHANES, (Korea) National Health and Nutrition Examination Survey.

To address the possible bias of selecting only adults≥40 years from KNHANES as spirometry was performed in this population, we conducted subgroup analysis on the two NHANES by excluding young adults aged≤39 years. The results were similar; an increase in HDL-C improved the lung function markers, FEV_1 and FVC, compared with other cholesterol markers (online supplemental table S3 in the supporting information).

We validated our results using a regression model from a previous study. Cirillo *et al*[9] preprocessed the measured absolute values of FEV_1 by dividing these values by height squared, which possibly enabled adjustment for the anthropometric effects on lung function while avoiding using reference equations. This model did not negate our study's results (online supplemental table S4 in the supporting information); a 1-SD increase in HDL-C resulted in a higher FVC (estimated increase: 14.6 mL (KNHANES), 45.7 mL (NHANES III), and 54.9 mL (NHANES 2007–2012)) and FEV_1 (estimated increase: 19.4 mL (KNHANES), 55.9 mL (NHANES III), and 59.6 mL (NHANES 2007–2012)). However, other cholesterol markers were not associated with height-normalised FVC or FEV_1.

We verified the robustness of our study with the reference lung function equation using nation-specific reference lung function equations rather than the GLI equations to calculate the percent predicted FVC and FEV_1. Different equations can result in significant differences in the predicted values of lung function, leading to different categorisations.[28] However, these different reference equations did not alter our results (online supplemental table S5 in the supporting information).

To rule out the potential influence of reverse causality stemming from participants with preexisting,

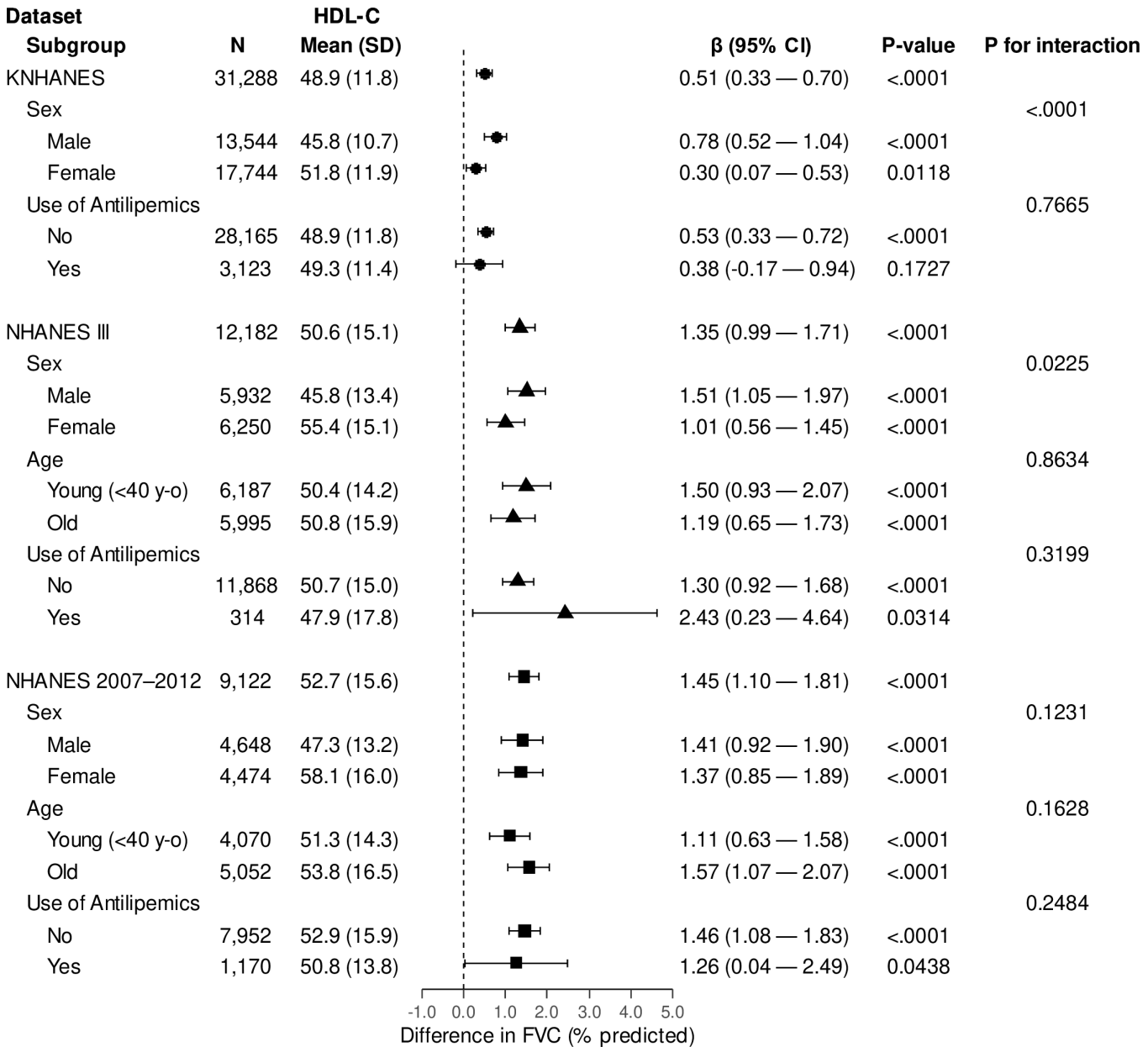

Figure 3 Subgroup analyses on the association between serum HDL-cholesterol level and FVC: based on age, sex, and use of lipid-lowering agents in three surveys. The correlation between serum HDL-cholesterol level and FVC was verified by subgroup analyses. The data from three surveys were analysed, stratifying by sex, age and use of antilipemics, using the linear regression model detailed in figure 2. For each subgroup, the figure displays the number of subjects, descriptive statistics for serum HDL-cholesterol, beta coefficients (for each 1-SD increase in serum HDL-cholesterol) with their 95% CIs, and p values. 'P for interaction' denotes the results of the heterogeneity test conducted across the subgroups. β, beta coefficient; FVC, forced vital capacity; HDL, high-density lipoprotein; (K)NHANES, (Korea) National Health and Nutrition Examination Survey.

yet uninvestigated respiratory diseases, we examined whether excluding subjects with incidental findings of abnormal spirometry patterns might impact the association between serum HDL-C levels and lung function. Exclusion of subjects with restrictive, obstructive, or mixed spirometry pattern, or any of the abnormalities did not affect the strong correlation between serum HDL-C level and lung function (online supplemental table S6 in the supporting information).

We applied various thresholds for categorising serum HDL-C levels to confirm the dose–response relationship between serum HDL-C level and FVC or FEV_1. The relationship between the HDL-C groups and the per cent predicted FVC consistently matched our earlier findings (online supplemental figure S2A in the supporting information). Additionally, the low HDL-C group exhibited a negative correlation with FEV_1 in all three surveys (online supplemental figure S2B in the

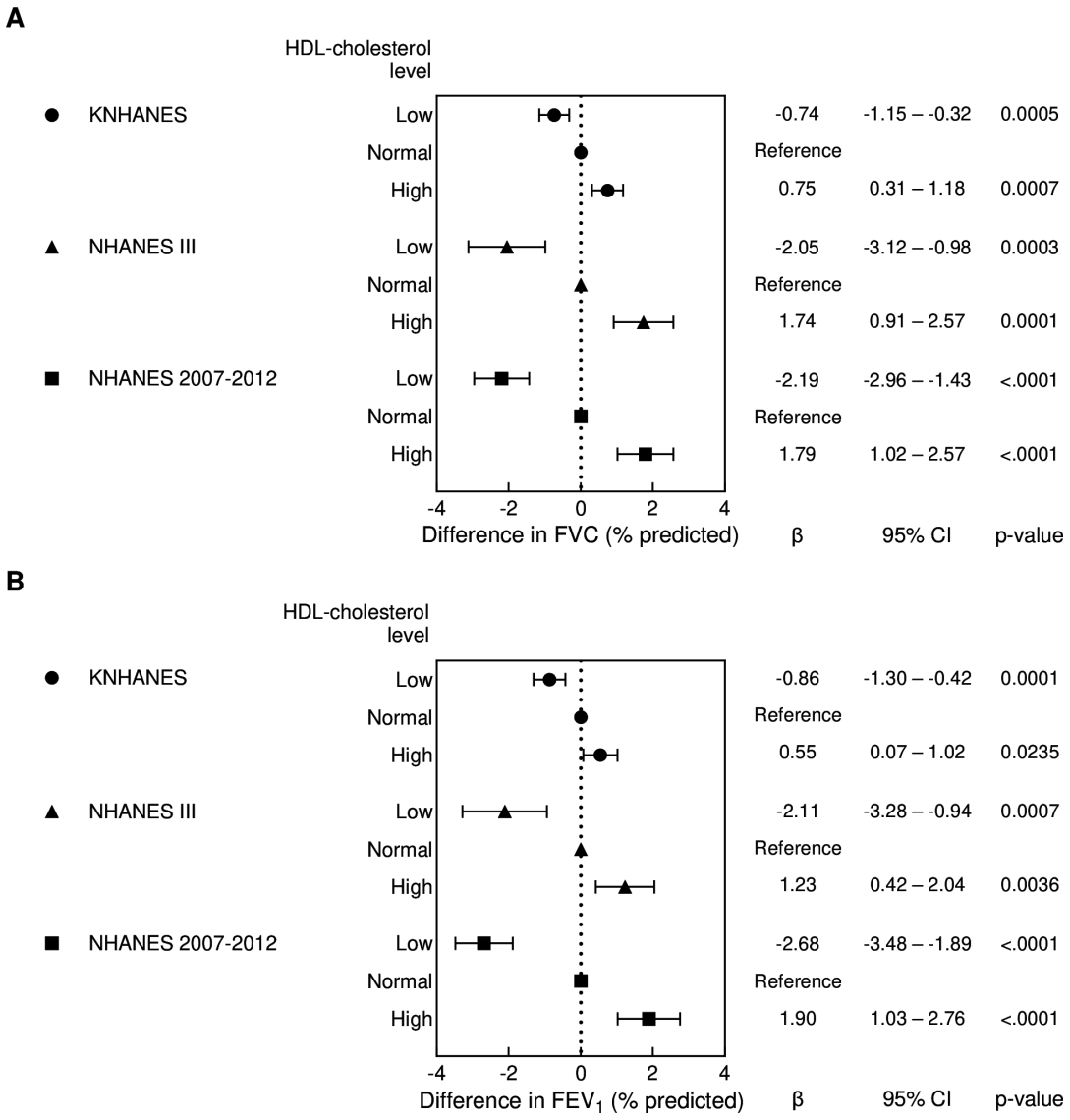

Figure 4 Estimated changes in lung function according to HDL-cholesterol groups. Estimated changes in the percent predicted (A) FVC and (B) FEV_1 were analysed with multivariate linear regression analysis. The regression coefficients and their 95% CIs with p values are presented. HDL-cholesterol levels were categorised into three groups: the normal (reference), low and high groups. Each model was adjusted for the following covariates: age, sex, household income in quartiles, body mass index (BMI), BMI^2, use of antilipidemic medicine, smoking pack year, and race (Black, Hispanic, White vs Asian, or others). The KNHANES dataset was not adjusted for race owing to the monoethnic nature of the study population. β, beta coefficient; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL, high-density lipoprotein; (K)NHANES, (Korea) National Health and Nutrition Examination Survey.

supporting information). However, the association of the high HDL-C group and FEV_1 varied among the surveys.

To evaluate the possibility of a non-linear relationship, particularly focusing on pronounced non-linear patterns in the extreme ranges, we further divided serum HDL-C levels into five groups based on the 5th, 35th, 65th and 95th percentiles and examined whether the linear trend persisted. Once again, the linear correlation between serum HDL-C and FVC or FEV_1 was consistently observed (online supplemental figure S3 in the supporting information).

DISCUSSION

To our knowledge, this is the first comprehensive analysis of three independent nationwide surveys investigating the association between HDL-C levels and lung function. Our study's results represent the adult populations of South Korea and the US in two different periods. Considering the large demographic differences between both countries and the time difference of 20 years between the two NHANES, we drew a robust and generalisable conclusion that serum HDL-C has a dose–response relationship with increased FVC and FEV_1, independent of age, sex, race, BMI, smoking status, use of antilipemic agents and socioeconomic status.

A previous study by Cirillo *et al*[9] based on NHANES III reported similar results to our study regarding the association between HDL-C and FEV_1. However, they did not evaluate the association with FVC or the dose–response relationship. Additionally, they did not exclude participants who failed the reproducibility criteria based on the quality assessment of spirometry. Therefore, we supplemented these points from a previous study and established that HDL-C was associated with both FVC and FEV_1.

Restrictive lung diseases are defined as a condition where FVC is decreased, which can be categorised by the aetiological origin: extrapulmonary diseases or pulmonary parenchymal diseases.[29] With the exclusion of malignancies and adjustment for age and BMI, common extrapulmonary causes, such as obesity and frailty, were corrected or excluded from the analyses. However, none of the surveys investigated the diagnosis of respiratory diseases other than asthma or COPD. This limitation was addressed through sensitivity analyses that excluded the subjects with incident findings of abnormal spirometry patterns. The exclusion of subjects with obstructive, restrictive or a combination of these abnormal spirometry patterns had no effect on the association between HDL-C and FVC, as well as HDL-C and FEV_1.

Recent discoveries on the role of cholesterol in the lungs have focused on the importance of cholesterol homeostasis. Reverse cholesterol transport is an in vivo mechanism by which peripheral tissues dispose of excess cholesterol via crosstalk with plasma lipoproteins.[30] Especially, HDL is the main target of macrophages and peripheral cells for cholesterol efflux and delivers cholesterol to the liver.[1] In previous studies, mouse models with a genetic deficiency in the synthesis of HDL or efflux of cholesterol had serious lung disorders, including susceptibility to infection, inflammation and accelerated loss of lung recoil with ageing.[6 7 31 32] Moreover, recent findings on the intracellular role of cholesterol have revealed that lysosomal cholesterol can control the activity of the mammalian target of rapamycin complex 1 signalling pathway, which is critical in lung fibrosis, mechanistic injury and inflammation.[33–36] These recent discoveries are consistent with a report from the Multi-Ethnic Study of Atherosclerosis, which confirmed that a decrease in HDL-C was associated with an increase in high-attenuation areas, a quantitative measure of subclinical interstitial lung disease using chest CT.[11]

Sexual differences significantly affected the association between HDL-C and lung function in KNHANES and NHANES III. It is not surprising that females had higher HDL-C levels in all three surveys. Even the median levels for women were higher than the upper tertiles for men. This difference in HDL-C levels may have contributed to a weaker association in females. Nevertheless, a positive correlation between HDL-C and FVC, as well as HDL-C and FEV_1 was consistently observed in females across all three surveys.

The potential role of lipid-lowering agents in modulating the association between HDL-C and lung function deserves consideration. While the primary objective of most lipid-lowering drugs is to reduce LDL-C levels, it is important to note that niacin, fibrates and certain statins have been reported to increase HDL-C levels as well.[37] In the US surveys, a comprehensive list of prescribed medications was obtained for all subjects. However, NHANES III lacked details on the specific constituents of medications prescribed for lipid management—a limitation partly explained by the fact that the first statin, lovastatin, was introduced to the market in 1987, just before NHANES III commenced in 1988.[38] Similarly, KNHANES relied on general questionnaires that identified if subjects were on medication for particular conditions but did not investigate the specifics of those medications. Consequently, the 'antilipemics' category in this study could encompass a variety of lipid-lowering drugs, each with distinct effects. This diversity complicates the interpretation of results concerning the HDL-C and lung function association. Nonetheless, we adjusted for the potential influence of these drugs in our regression models, and the observed interaction effects with this variable were minimal.

The main strength of this study lies in its design. NHANES is a well-validated nationwide survey with strict quality control. We used two 6-year periods from NHANES: 1988–1994 and 2007–2012. Considering the two-decade interval between both surveys, the demographic distribution and health-related behaviour varied; therefore, independence between the two US surveys is guaranteed. Moreover, since there are few Asians in the USA, these two surveys may not sufficiently represent the phenotypes of Asians and their lifestyles. We addressed this vulnerability using KNHANES data. Using the Taylor series method, the representativeness of these nationwide surveys was not compromised. Furthermore, through detailed subgroup and sensitivity analyses, which compared the results of the three surveys, we reached a robust conclusion that may be applicable to other countries with different racial distributions.

This study has several limitations. First, its cross-sectional design restricts us from establishing a causal relationship between HDL-C and lung function. Lifestyle factors and/or preexisting diseases in lifetime could potentially confound the observed association.[39] While our study may not have comprehensively addressed all potential confounding factors, it is noteworthy that we have undertaken measures to mitigate the influence of reverse causality stemming from reported respiratory diseases, as well as the presence of incidental spirometry abnormalities.

Second, we analysed limited types of cholesterol and lipoproteins. For example, HDL-C can be further classified by size or apolipoprotein composition.[40] Apolipoprotein A-I, the primary component of HDL-C, has been reported to reduce lung fibrosis and emphysema in animal models while also being associated with improved lung function in a cross-sectional study.[9 41 42]

Due to data availability, serum lipid profiles (eg, total cholesterol, LDL-C and HDL-C) were exclusively used throughout this study. Nevertheless, an analysis on the association between apolipoprotein A-I and lung function in NHANES III yielded results consistent with those for HDL-C (online supplemental table S7 in the supporting information). Although this data limitation may potentially restrict the interpretation of our results regarding biological mechanisms, our results have wide applicability since serum cholesterol measurements are common and easy to access.

Lastly, recent studies have shown a J-shaped or U-shaped dose–response relationship between HDL-C and mortality.[43 44] In our analysis, we highlighted the general range of HDL-C with assumption of a linear association, potentially neglecting the non-linear effect of HDL-C on the low and high extreme ranges. However, the linear relationship between HDL-C and FVC or HDL-C and FEV_1 did not change, even when the analysis was performed with more finely divided categorical variables. Ultimately, longitudinal cohort studies and randomised clinical trials are required to verify the true causal effect of HDL-C on lung function decline and possibly on pulmonary diseases.

In conclusion, high HDL-C levels were associated with improved FVC and FEV_1 in three nationwide cross-sectional studies from the USA and South Korea. However, further studies are needed to confirm this association and elucidate the underlying mechanisms.

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