Relationship between Lipoprotein(a) and Lung Function assessed in Community-Dwelling Older Adults: Longitudinal and Cross-Sectional Analyses

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Research Article

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Abstract

Background: Lipoprotein(a) [Lp(a)] has recently been gaining increasing interest, with numerous studies pointing to a causal relationship with cardiovascular disease, coronary heart disease, as well as aortic valve stenosis. However, so far only a few studies have assessed the association between Lp(a) and pulmonary health and there have been some inconsistent findings regarding this topic. This study's aim is to examine whether high level of serum Lp(a) is associated with better lung function in a dataset of relatively healthy older women and men in a sex-specific manner.

Methods: We used the longitudinal data collected at two time points 7.4 ±1.5 years apart from 679 participants (52% females, 68 [65-71] years old) in the Berlin Aging Study II (BASE-II). Several lipid parameters, including Lp(a), and lung function were measured in these subjects as part of a comprehensive medical assessment. The baseline dataset was collected between 2009 to 2014, and the follow-up data were collected between 2018 and 2020. Multiple linear regression models adjusting for covariates (BMI, physical inactivity, smoking status, alcohol intake, and a morbidity index) were applied to strengthen evidence for the relationship observed between Lp(a) and lung function in a sex-specific manner.

Results: Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were higher in men and declined with age in both sexes. Men had lower Lp(a) levels than women. Average lung function measurements were higher in both men and women with higher Lp(a) levels. However, this association was statistically apparent in men only.

Conclusions: The data suggest that Lp(a) might act as a protective and possibly sex specific factor in pulmonary health, a putative role which has not been anticipated so far. Future studies will be required to further establish the relationship between Lp(a) and lung function also with regard to possible causality and sex differences, as well as to further investigate the exact function Lp(a) plays in lung physiology.

Introduction

Discovered by the Norwegian physician Kare Berg in 1963, lipoprotein(a) [Lp(a)] is composed of a LDL-like particle with an apolipoprotein B100 component covalently bound to an apolipoprotein(a) particle [1–8]. Over the last decade, numerous clinical data have shown that increased serum Lp(a) concentrations were associated with higher risk of cardiovascular disease (CVD) [9–12]. Furthermore, mendelian randomization and large epidemiological studies have accumulated strong evidence for Lp(a) acting as the single most common independent genetically inherited causal risk factor for CVD [13–15]. These compelling and consistent findings regarding the stark association between Lp(a) and cardiovascular events have generated high interest amongst researchers and physicians in understanding the pathogenicity of Lp(a) and discovering new lipid-lowering agents specifically targeted to lower Lp(a) concentration [16–20]. However, the physiological function of Lp(a) remains for the most part unclear, especially regarding its role in pulmonary health.

Impaired lung function is known to be associated with coronary artery disease, cardiovascular disease, stroke, and cardiovascular mortality, as well as all-cause mortality independent of cardiac function and other cardiovascular risk factors [21]. The close interrelationship between pulmonary and cardiovascular pathophysiology [22–25] raises the question whether Lp(a) could also be a clinical risk factor for pulmonary health.

There are only two studies so far that have investigated the direct relationship between Lp(a) and pulmonary health in the general population [26, 27]. Both studies utilized spirometry in order to assess general lung health. Spirometry is a lung function test that measures, among other parameters, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), and is the most common pulmonary function test used to detect and monitor chronic lung diseases [28]. According to our previous analyses of cross-sectional data from the Berlin Aging Study II (BASE-II) (n = 606, 55.1% females, 68 [60–84] years old), high serum Lp(a) levels were associated with higher FEV1 in older men [26]. Conversely, a cross-sectional study by Lee and colleagues in 2017 (n = 64082, 48.4% females, 38±7 years old) showed that high Lp(a) levels were associated with lower FEV1 as well as lower FVC in a large study population consisting of Korean health screening subjects [27]. As a result of these inconsistent findings and a clear lack of other studies, the relationship between Lp(a) and lung function remains to be further investigated.

Therefore, in the present study we conducted a follow-up analysis using Lp(a) concentrations measured at baseline in the BASE-II [29], and newly measured spirometry measurements which was assessed in BASE-II participants as part of the GendAge study [30]. Our aim was to determine whether high Lp(a) level at baseline is also longitudinally associated with better lung function assessed on average 7.4 years later in mostly community-dwelling older people and whether this associations is sex specific.

Materials And Methods

Study participants

The data analyzed in the current study were collected from participants of the Berlin Aging Study II (BASE-II) including follow-up data which were assessed as part of the GendAge study 7.4 ± 1.5 years later [29–31]. Launched in 2009, BASE-II comprises a convenience sample and the study aims to investigate factors of “healthy” versus “unhealthy” aging in residents of the greater Berlin, Germany. In order to understand the complex and multifaceted aspects of aging, this multidisciplinary study encompasses a wide range of disciplines, such as geriatrics, immunology, psychology, genetics, biology, sociology, as well as economics. A wide variety of data was collected from a cohort of 1600 elderly subjects aged 60 to 80 and a
control group of 600 younger adults aged 20 to 35, which was not considered in the current analysis. The cross-sectional baseline examination was completed in 2014 [29].

In total 1,083 BASE-II participants of the older group were medically re-examined between June 2018 and March 2020 as part of the GendAge study [31]. We additionally considered 17 participants who completed assessments in the GendAge study without medical baseline data available (these 17 participants are part of the BASE-II sample and were examined at least at one of the other BASE-II study sites). The cohort analyzed in the current study is larger than and does not completely overlap with the cohort in the study by Buchmann et al [26]. We aimed to improve the quality of spirometry testing for the follow-up study and were thus able to achieve a greater number of subjects with good quality spirometry measurements in our current cohort. All participants gave written informed consent and the Ethics Committee of the Charité – Universitätsmedizin Berlin approved the study (approval numbers EA2/029/09 and EA2/144/16).

Exclusion criteria

In accordance with the criteria from our previous analyses from BASE-II, we have excluded subjects who were younger than 60 years old at baseline, those with a spirometry test quality lower than grade "C", and those who answered "yes" or "I don't know" when asked about being diagnosed with bronchial asthma [26]. We further excluded subjects with missing Lp(a) data from baseline and missing lung function measurements (i.e. FEV1 and FVC) from the follow-up assessments. This resulted in a total of 679 older subjects analyzed in the current study (Fig. 1).

Lipoprotein(a) measurement

Blood samples were extracted after >8 hours of fasting and kept at 4–8 degrees Celsius until analyzed on the same day. Concentration of Lp(a) was measured using immunological turbidity tests in a certified laboratory (Labor Berlin GmbH). Lipoprotein(a) concentrations lower than the detection limit of 30mg/L or 7mmol/l were set to 15mg/l or 3.5mmol/l, respectively.

Measurement of pulmonary function at follow-up

Spirometry was performed as recommended by the American Thoracic Society using the EasyOne™ Spirometer (ndd Medizintechnik AG, Zurich, Switzerland) [28]. A minimum of two spirometry measurements with a sufficient level of quality had to be available, with the difference of the two highest FEV1 and FVC values being less than or equal to 200ml (categorized as quality grade A, B, or C) to be included in the current analysis. The highest FEV1 and FVC values from three or more tests with sufficient level of quality were used for the analysis.

Covariables

Body weight for the BMI calculation was measured in minimal clothing to the nearest 0.1 kg, and height was measured to the nearest 0.1cm using an electronic weighing and measuring station (seca 764, seca, Hamburg, Germany). Standardized questions were used to assess the following covariables: Smoking status was categorized dichotomously as either currently smoking or currently not smoking, which included previous smokers. For alcohol intake, participants were asked if they consume alcohol regularly (either "yes" or "no"), and for assessment of physical activity, participants were asked if they are rarely or never physically active (either "yes" or "no").

Comorbidities and morbidity burden of the participants was evaluated using a morbidity index (MI) largely based on the categories of the Charlson Comorbidity Index [32]. Multiple diagnoses were used to calculate the MI and these diagnoses were obtained mainly through assessment of medical history by the study physician. The MI, ranging from 0 to 10 is a weighted sum of moderate to severe, mostly chronic illnesses, including but not limited to cardiovascular (e.g. congestive heart failure), cancer (e.g. lymphoma), pulmonary (e.g. chronic obstructive pulmonary disease), and metabolic diseases (e.g. type 2 diabetes mellitus). HIV and peptic ulcer disease were not included in the calculation of the MI. Prevalence of type 2 diabetes mellitus (T2D) was determined based on the guidelines of the American Diabetes Association [33], considering self-reported history of diabetes, laboratory measurements (fasting glucose and results from an oral glucose tolerance test in participants with an unknown history of T2D, and diabetes-specific medication. Metabolic syndrome (MetS) was defined by using the criteria suggested by Alberti et al [34].

Statistical analysis

Continuous variables are presented as mean with standard deviation (± SD) or median with interquartile range (IQR). Categorical variables are presented as absolute number and percentage. Kolmogorov-Smirnov test was used to determine normal distribution. Student's t-test was used for normally distributed data and Mann-Whitney-U-Test for skewed data when comparing the differences between two groups. Categorical variables between two groups were compared using Chi-square test or Fisher's exact test. Paired Student's t-test (for normally distributed data), Wilcoxon signed-rank test (for skewed data), and McNemar's test (for binominal data) were used when comparing the variables of two related samples (baseline versus follow-up). Baseline serum Lp(a) concentration values were divided into quintiles and categorized into dichotomous groups – low Lp(a) concentration as Lp(a) quintile 1 and high Lp(a) concentration as Lp(a) quintiles 2–5. Multiple linear regression was executed a) to investigate the association of serum Lp(a) level at baseline (predictor variable) and lung function at follow-up (outcome variable), and b) to adjust for confounding covariables. Here, Lp(a) quintile 1 and Lp(a) quintiles 2–5 were used as binary variables, in which the low Lp(a) group (Lp(a) quintile 1) was tested against the high Lp(a) group (Lp(a) quintiles 2–5). Model 1 was adjusted for age. In model 2, lifestyle factors (smoking status, alcohol consumption, self-reported physical inactivity, and BMI) were added. In model 3, we additionally adjusted for morbidity (morbidity index). One-way analysis of covariance (ANCOVA) and 95% confidence interval was used to determine the differences in the adjusted means of lung function
measurements of each Lp(a) quintile group 1 through 5. Men and women were analyzed separately for all tests. All analyses in this study are explorative, resulting p-values are interpreted descriptively. These statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, USA).

Results

Descriptive characteristics of baseline data and lung function measurements at follow-up

Characteristics of participants captured at baseline and lung function at follow-up are summarized in Table 1. In the baseline examination Lp(a) was measured in 1,584 participants aged 60 years and older, 679 of these participants underwent a successful lung function test at follow-up 7.4 ± 1.5 years later. At baseline, women had a higher median Lp(a) level (120mg/L [50–420]) than men (90mg/L [40–210]) (p = 0.002) and a lower median BMI of 25.1kg/m² (22.9–28.0) (p < 0.001) than men 26.9kg/m² (24.8–29.0). There were no statistically apparent differences in age, smoking status, regular alcohol intake, self-reported physical inactivity, and morbidity index between men and women at baseline (Table 1). As expected, men had a higher mean FEV1 and FVC than women, whereas the median FEV1/FVC was higher in women (p < 0.001, Table 1).

Table 1

| Characteristics of participants at baseline and lung function measurements at follow-up 7.4 ± 1.5 years later. |
|-------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                                 | All (n = 679)                  | Men (n = 326)   | Women (n = 353) | p-value*        |
| Age [years]                                     | 68 (65–71)                    | 68 (65–71)      | 68 (65–70)      | 0.108           |
| BMI [kg/m²]                                     | 26.2 (23.8–28.7)              | 26.9 (24.8–29.0)| 25.1 (22.9–28.0)| < 0.001         |
| Current smoker [n;%]                            | 61 (9)                        | 30 (9)          | 31 (9)          | 0.894           |
| Regular alcohol intake [n;%]                    | 611 (90)                      | 297 (91)        | 314 (89)        | 0.289           |
| Self-reported physical inactivity [n;%]         | 55 (8)                        | 33 (10)         | 22 (6)          | 0.066           |
| Morbidity index [pts.]                          | 1 (0–2)                       | 1 (0–2)         | 0 (0–1)         | 0.052           |
| T2D [n;%]                                       | 74 (11)                       | 52 (16)         | 22 (6)          | < 0.001         |
| MetS [n;%]                                      | 230 (34)                      | 141 (44)        | 89 (26)         | < 0.001         |
| Lipoprotein(a) [mg/l]                           | 106 (50–281)                  | 90 (40–210)     | 120 (50–420)    | 0.002           |
| Follow-up                                       |                               |                 |                 |                 |
| FEV1 [ml]                                       | 2337 ± 615                    | 2737 ± 563      | 1967 ± 387      | < 0.001         |
| FVC [ml]                                        | 3115 ± 798                    | 3686 ± 671      | 2588 ± 480      | < 0.001         |
| FEV1/FVC [%]                                    | 76 (72–79)                    | 75 (71–79)      | 76 (73–80)      | < 0.001         |

Results are shown as mean ± SD for variables with a normal distribution or median (interquartile range) for variables with a skewed distribution

*Student’s t-test for normally distributed data or Mann-Whitney-U-Test for skewed data

Descriptive characteristics comparing baseline and follow-up data

Changes between baseline and follow-up characteristics were determined by comparing the paired values from the two assessments (Table 2). In men, average BMI and self-reported physical inactivity did not change meaningfully after 7.4 ± 1.5 years (p = 0.136 and p = 0.401, respectively), while in women the average BMI increased from 25.1kg/m² (22.9–28.0) to 25.5 kg/m² (23.0-28.7) (p < 0.001). Self-reported physical inactivity increased in women after 7.4 years (p = 0.028). The proportion of men as well as women currently smoking and drinking alcohol decreased, and the morbidity index increased after 7.4 years. In men, there was a relevant change in the distribution of those categorized in Lp(a)-quintile 1 after 7.4 ± 1.5 years (20% at baseline vs 25% at follow-up with Lp(a) below the detection limit, p = 0.010) In women, this distribution did not change after 7.4 years.
Table 2
Characteristics of subjects with longitudinal data available at baseline and at follow-up (paired comparison)

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 326)</th>
<th>Women (n = 353)</th>
<th>All (n = 679)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>p-value*</td>
</tr>
<tr>
<td>Age [years]</td>
<td>68 (65–71)</td>
<td>76 (72–78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>26.9 (24.8–29.0)</td>
<td>26.8 (24.7–29.1)</td>
<td>0.136</td>
</tr>
<tr>
<td>Current smoker [n; %]</td>
<td>30 (9)</td>
<td>16 (5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Regular alcohol intake</td>
<td>297 (91)</td>
<td>275 (84)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Self-reported physical inactivity [n; %]</td>
<td>33 (10)</td>
<td>41 (13)</td>
<td>0.401</td>
</tr>
<tr>
<td>Morbidity index [pts.]</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GGT [U/l]</td>
<td>25 (19–37)</td>
<td>27 (20–37)</td>
<td>0.033</td>
</tr>
<tr>
<td>ALT [U/l]</td>
<td>22 (17–28)</td>
<td>21 (17–27)</td>
<td>0.559</td>
</tr>
<tr>
<td>AP [U/l]</td>
<td>58 (51–70)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lp(a) [mg/l]</td>
<td>90 (40–210)</td>
<td>82 (34–190)</td>
<td>0.354</td>
</tr>
<tr>
<td>Lp(a) quintile 1 [n; %]</td>
<td>65 (20)</td>
<td>82 (25)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SD for variables with a normal distribution or median (interquartile range) for variables with a skewed distribution

*Paired Student’s t-test (for normally distributed data), Wilcoxon signed-rank test (for skewed data), or McNemar’s test (for binominal data)

Furthermore, Table 3 and Fig. 2 present the difference in mean FEV1 and FVC from baseline and follow-up, illustrating the decline in pulmonary function after 7.4 years. A total of 356 participants had a paired set of lung function measurements from both baseline and follow-up that also met the spirometry quality criteria. Of these 356 participants, men had a mean FEV1 of 3064 ± 521 ml at baseline and 2733 ± 551 ml at follow-up, and women had a mean FEV1 of 2228 ± 418 ml at baseline and 1958 ± 404 ml at follow-up. As expected, FEV1 and FVC decreased with age in both sexes (p < 0.001), while FEV1/FVC ratio did not show a meaningful change over time.

Table 3
Lung function measurements at baseline and follow-up (paired comparison)

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 173)</th>
<th>Women (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>FEV1 [ml]</td>
<td>3064 ± 521</td>
<td>2733 ± 511</td>
</tr>
<tr>
<td>FVC [ml]</td>
<td>4195 ± 671</td>
<td>3707 ± 647</td>
</tr>
<tr>
<td>FEV1/FVC [%]</td>
<td>74 (69–78)</td>
<td>74 (70–78)</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SD for variables with a normal distribution or median (interquartile range) for variables with a skewed distribution

*Student’s t-test for normally distributed data or Mann-Whitney-U-Test for skewed data

Descriptive characteristics according to low vs high Lp(a)

Characteristics of participants captured at baseline and lung function at follow-up according to low vs high Lp(a) group (Lp(a)-quintile 1 vs Lp(a)-quintiles 2–5) are summarized in Table 4. Men in Lp(a)-quintiles 2–5, with a median Lp(a) concentration of 129 mg/L (70–280), showed higher FEV1 and FVC measurements at follow-up (2776 ± 555 ml and 3728 ± 676 ml, respectively), compared to those in Lp(a)-quintile 1 (2577 ± 570 ml and 3520 ± 630 ml, respectively) (p = 0.010 and p = 0.026, respectively). The distributions of lung function measurements according to Lp(a)-quintile 1 and Lp(a)-quintiles 2–5 are illustrated in Fig. 3. In women, mean FEV1 and FVC were slightly higher in Lp(a)-quintiles 2–5 compared to those of women in Lp(a)-quintile 1. While these measurements showed a similar trend as those of men, there was no statistical difference in the lung function between the low vs high Lp(a) group in women. The difference in FEV1/FVC ratio between low vs high Lp(a) groups was not statistically apparent in both men and
women. Other baseline characteristics (i.e., age, BMI, smoking status, regular alcohol intake, self-reported physical inactivity, and morbidity index) did not differ statistically between low Lp(a) vs high Lp(a) group.

Table 4
Lp(a) quintile 1 vs 2–5: Participants’ characteristics at baseline and lung function at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 326)</th>
<th>Women (n = 353)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a) quintile 1</td>
<td>67 (65–71)</td>
<td>68 (65–70)</td>
<td>68 (65–70)</td>
</tr>
<tr>
<td>Lp(a) quintile 2–5</td>
<td>69 (66–71)</td>
<td>68 (65–71)</td>
<td>68 (66–71)</td>
</tr>
<tr>
<td><strong>Age [years]</strong></td>
<td>67 (65–71)</td>
<td>68 (65–70)</td>
<td>68 (66–71)</td>
</tr>
<tr>
<td><strong>BMI [kg/m2]</strong></td>
<td>27.2 (24.5–29.5)</td>
<td>26.9 (24.9–29.0)</td>
<td>26.0 (23.8–28.7)</td>
</tr>
<tr>
<td><strong>Current smoker [n; %]</strong></td>
<td>9 (14)</td>
<td>7 (10)</td>
<td>14 (11)</td>
</tr>
<tr>
<td><strong>Regular alcohol intake [n; %]</strong></td>
<td>57 (88)</td>
<td>65 (93)</td>
<td>115 (91)</td>
</tr>
<tr>
<td><strong>Self-reported physical inactivity [n; %]</strong></td>
<td>9 (14)</td>
<td>5 (7)</td>
<td>14 (11)</td>
</tr>
<tr>
<td><strong>Morbidity index [pts]</strong></td>
<td>1 (0–2)</td>
<td>0 (0–1)</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td><strong>T2D [n; %]</strong></td>
<td>15 (23)</td>
<td>8 (12)</td>
<td>23 (17)</td>
</tr>
<tr>
<td><strong>MetS [n; %]</strong></td>
<td>28 (43)</td>
<td>22 (32)</td>
<td>50 (37)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 [ml]</td>
<td>2577 ± 570</td>
<td>1936 ± 380</td>
<td>2293 ± 576</td>
</tr>
<tr>
<td>FVC [ml]</td>
<td>3520 ± 630</td>
<td>2541 ± 461</td>
<td>3084 ± 731</td>
</tr>
<tr>
<td>FEV1/FVC [%]</td>
<td>74 (70–78)</td>
<td>77 (72–80)</td>
<td>76 (71–79)</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SD for variables with a normal distribution or median (interquartile range) for variables with a skewed distribution

*Student’s t-test for normally distributed data or Mann-Whitney-U-Test for skewed data

Multiple linear regression models assessing the association between baseline Lp(a) and follow-up lung function measurements

To assess whether low Lp(a) concentration at baseline is independently associated with lower lung function 7.4 years later, we performed multiple linear regression analyses with adjustments for baseline covariables that may affect lung function outcome (Table 5). Model 1 was adjusted for age.

In model 2, the lifestyle factors smoking status, regular alcohol intake, self-reported physical inactivity, and BMI were added. The morbidity index, which encompasses T2D diagnosis and chronic obstructive pulmonary disease (COPD) amongst other chronic illnesses, was added in model 3. In men, low Lp(a) level [Lp(a)-quintile 1] was strongly associated with lower levels of FEV1 and FVC throughout all three models. According to the highest adjusted model 3, low serum Lp(a) levels (quintile 1) were associated with 213ml and 222ml lower levels of FEV1 (p = 0.007) and FVC (p = 0.017), respectively, in men, when compared to these parameters in men with higher Lp(a) levels (quantiles 2–5). In women, the baseline Lp(a) level showed no association with lung function assessed 7.4 years later. Recalculation of models 1 to 3 using covariables measured at follow-up further showed a statistically supported association between low Lp(a) level and lower FEV1 and FVC in men, but no evidence for this association was found in women (data not shown).
The results presented in this follow-up study reaffirm our previous findings [26] and

<table>
<thead>
<tr>
<th>Lp(a) quintile</th>
<th>Men</th>
<th>FVC</th>
<th>FEV1/FVC</th>
<th>Women</th>
<th>FVC</th>
<th>FEV1/FVC</th>
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<tbody>
<tr>
<td></td>
<td>FEV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beta</td>
<td>SE</td>
<td>p</td>
<td>Beta</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Model 1</td>
<td>-225</td>
<td>74</td>
<td>0.003</td>
<td>-237</td>
<td>89</td>
<td>0.008</td>
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<tr>
<td>Model 2</td>
<td>-210</td>
<td>74</td>
<td>0.005</td>
<td>-219</td>
<td>87</td>
<td>0.013</td>
</tr>
<tr>
<td>Model 3</td>
<td>-213</td>
<td>78</td>
<td>0.007</td>
<td>-222</td>
<td>92</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*调整Lp(a) quintile 1和Lp(a) quintiles 2–5用于将低Lp(a)组与高Lp(a)组进行比较

**多变量回归分析: Lp(a) quintile 1在基线和随访时与肺功能的关系**

为了进一步确定基线Lp(a) quintile 1中是否存在任何差异，我们进行了一项一元方差分析(分析方差)。通过年龄、BMI、酒精摄入量、吸烟状况、自我报告的体力活动以及疾病指数等变量，我们对基线Lp(a) quintile 1进行了调整。基线Lp(a) quintile 1的估计平均FEV1和FVC值在所有结果中均较低。男性在Lp(a) quintile 3中显示了最高的肺功能测量值，而女性在Lp(a) quintile 3中显示了最高的估计平均FEV1和FVC值。对于IFV1/FVC值，Lp(a) quintile 3显示了最高的肺功能测量值，估计平均值为2835ml (95% CI [2686, 2984]) 和FVC为3761ml (95% CI [3591, 3941])，与Lp(a) quintile 1的平均值相比分别高276ml和254ml。与Lp(a) quintile 1相比，Lp(a) quintile 4和5的估计平均FEV1和FVC值略低于Lp(a) quintile 3，但仍然高于Lp(a) quintile 1。男性在Lp(a) quintile 4和5中显示了统计上显著的差异，在调整后的FEV1和FVC值中，Lp(a) quintile 1与2、3、4、5之间的差异在0.05以下。同样地，女性从Lp(a) quintile 3中显示了最高的估计平均FEV1和FVC值，而女性从Lp(a) quintile 1中显示了最低的平均肺功能测量值。

**交叉分析: 评估重新评估的Lp(a)和肺功能测量结果**

与基线Lp(a) quintile 1 vs Lp(a) quintiles 2–5和多个线性回归分析中重新评估的基线Lp(a)和肺功能测量数据，以及基线Lp(a)和肺功能测量数据的方差分析(分析方差)。在基线Lp(a) quintile 1中显示出最低的估计平均FEV1和FVC测量值。男性在Lp(a)-quintile 1中显示了最低的估计平均FEV1和FVC测量值。在Lp(a) quintile 1中，男性显示了最高的肺功能测量值，而女性显示了最高的偿还FEV1和FVC测量值，而女性从Lp(a) quintile 1中显示了最低的平均肺功能测量值。

**讨论**

在本研究中，我们使用了679名60岁以上社区居住的参与者在基线和随访期间的纵向数据，以分析基线Lp(a)浓度和基线肺功能测量之间相隔10.5年的相关性。

## 表5: Lp(a) quintile 1 at baseline and lung function at follow-up

<table>
<thead>
<tr>
<th>Lp(a) quintile</th>
<th>FEV1</th>
<th>FVC</th>
<th>FEV1/FVC</th>
<th>FEV1</th>
<th>FVC</th>
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<td>SE</td>
<td>p</td>
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<td>SE</td>
<td>p</td>
</tr>
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<td>0.003</td>
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<tr>
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<td>0.005</td>
<td>-219</td>
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<td>0.013</td>
</tr>
<tr>
<td>Model 3</td>
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<td>78</td>
<td>0.007</td>
<td>-222</td>
<td>92</td>
<td>0.017</td>
</tr>
</tbody>
</table>

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## 讨论

在本研究中，我们使用了679名60岁以上社区居住的参与者在基线和随访期间的纵向数据，以分析基线Lp(a)浓度和基线肺功能测量之间相隔10.5年的相关性。
expand the existing knowledge based on cross-sectional data by using a longitudinal approach to establish the directionality of the relationship between Lp(a) and pulmonary function. Furthermore, we observed a statistically apparent decline in lung volumes (FEV1 and FVC) in both sexes between the two measurements (baseline and follow-up), highlighting the age-associated changes in pulmonary function. These age-associated changes lead to reduced lung function, diminished pulmonary remodeling and regenerative capacity, and increased susceptibility to pulmonary diseases [35–38]. Pulmonary diseases have significant consequences for the aging population, as they are the third leading cause of death in people aged 65 and older [39]. Taking into consideration the importance of pulmonary function for longevity and the ever-growing aging population, there is a clinical interest in understanding aging process of the lung and identifying early signs of lung function deterioration — especially in the older population.

In addition to our previous study based on cross-sectional BASE-II baseline data [26], there is only one other study so far that analyzed the relationship between Lp(a) and lung function in a population-based cohort. Contrary to our findings, the cross-sectional study by Lee et al. observed an inverse association, in which reduced lung function was associated with elevated Lp(a) levels in a cohort of 64,082 Korean health screening examinees [27]. Several factors could account for the incongruent results regarding the Lp(a)-lung function relationship. The mean age of the enrolled participants in their study was 38 ± 7 years, considerably younger than the median age of the current study (68[65–71] years at baseline, 76[73–78] years at follow-up). The authors of the study speculated that due to the higher mean age, our cohort may have included more subjects with subclinical hepatic dysfunction, which could have affected Lp(a) levels, as Lp(a) is synthesized exclusively by the liver [4, 40]. Although age-related changes in hepatic structure and function have been described [41], hepatic function seems to be quite well maintained in old age [42]. Our study included generally healthy participants with liver related parameters such as gamma-glutamyl transferase (GGT), alanin amino transferase (ALT), and alkaline phosphatase (ALP) on average within the clinical normal range at both baseline and follow-up (Table 2) [43]. Furthermore, the observed association between low Lp(a) level and lower lung function measurements was statistically stable even after adjustments for GGT, ALT, and ALP (Model 6, Supplementary Table 3, Additional File 4). The results of these follow-up analyses suggest that an age-related reduction of liver function is unlikely to explain the observed relationship between Lp(a) and lung function.

Notably, our cohort consists of participants of European ancestry, whereas the study by Lee et al. consisted of Korean participants. Several studies have demonstrated ethnic differences in Lp(a) levels due to genetic variations across ethnic groups [44].

Furthermore, two studies in the past have assessed the association between Lp(a) levels and pulmonary function in a clinical setting, specifically in COPD patients. In a group of 90 COPD patients and a control group of 90 healthy subjects, Lp(a) levels were significantly higher in the COPD group [45]. Another study compared 20 COPD patients with 20 healthy subjects but found no difference in Lp(a) concentrations between the two groups. Due to the limited sample size, these studies are, however, not suited to draw reliable conclusions on the association between Lp(a) and COPD [46].

Given that both impaired lung function and high Lp(a) levels are recognized risk factors for cardiovascular disease (CVD), the positive relationship between Lp(a) and lung function observed in our study seemed at first inconsistent. However, several studies have also demonstrated rather unexpected relationships between Lp(a) and risk factors of CVD, which stand in marked contrast to prior studies that have shown a positive association of Lp(a) with CVD. A number of studies, including BASE-II, reported low levels of Lp(a) being associated with higher risk of T2D and MetS [47–53]. The association between low Lp(a) and lower lung function observed in the current study is in accordance with such findings, as both T2D and MetS are also known to be associated with decreased lung volumes [54–56]. In the BASE-II sub-cohort studied here, the prevalence of T2D was higher in low Lp(a) group than in high Lp(a) group (p = 0.010), but there was no statistically apparent difference between the two groups regarding the prevalence of MetS (Table 4). Further adjustments for T2D and MetS as covariables had no meaningful impact on the association between Lp(a) and lung function (Model 4 and 5, Supplementary Table 3, Additional File 4). However, this does not rule out the possibility that Lp(a) levels are causally linked to the increased risk of T2D, MetS, and decreased lung function as observed here. Onat and colleagues postulated enhanced inflammation and autoimmune activation may result in reduced circulating Lp(a) due to “trapping” of Lp(a) by immune complex formation, yielding reduced assayed Lp(a) concentration [57]. According to this notion, low Lp(a) level may have resulted from inflammation related mechanism associated with T2D, MetS, and lung function impairment.

The physiological function and exact mechanisms that underlie the role of Lp(a) in lung function remain unclear. Emerging studies regarding the role of cholesterol and lipoproteins in lung surfactant suggest a possible link between lipoprotein molecules and lung (patho)physiology [58–66]. Lipid tracer studies in rodents estimated that more than 80% of surfactant cholesterol is derived from serum lipoproteins, highlighting the possibility that dyslipidemia in humans may dysregulate lipid composition of the lung surfactant, a vital component for a healthy lung function. Furthermore, circulating lipoproteins, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein (VLDL), play a vital role in normal lung function, as they are known to affect both the synthesis and secretion of lung surfactant [67, 68]. In a study by Barochia et al., HDL-C and apolipoprotein A1 (apoA-I) were positively correlated with FEV1, whereas LDL-C, triglycerides, apolipoprotein B (apoB), and apoB/apoA-I ratio were negatively correlated with FEV1 among patients with atopic asthma [59].

In addition, it appears that the relationship between Lp(a) concentration and lung function is not linear. When analyzing the mean FEV1 and FVC of the individual Lp(a) quintiles 1 to 5 in ascending order, men with moderately high Lp(a) values (Lp(a)-quintile 3) showed the highest mean FEV1 and FVC values. Lung function measurements from each Lp(a)-quintile 2 to 4 were higher than those of Lp(a)-quintile 1 in men. While the underlying mechanism of this relationship remains unclear, this may indicate that a moderately high Lp(a) concentration, and perhaps not necessarily a very high Lp(a) concentration, could have a beneficial role in lung function.
The directionality of the Lp(a)-lung function relationship observed in women was similar to that of men, but there was no statistically supported difference in the lung function measurements between the low versus high Lp(a) group in women. This “weaker” relationship in women compared to men was also observed in our previous study [26], and the reasons for the differing results are likely multifactorial and due to sex-related differences in Lp(a) and lung health. Firstly, changes in Lp(a) levels behave differently in men and women with age. Siomony et al. compared the sex-specific changes in Lp(a) levels across different ages and observed that while the increase in Lp(a) levels by age was steady in men, there was an additional modest increase around age 50 in women, resulting in significantly higher Lp(a) levels in women than in men [69]. Several studies support the findings that Lp(a) levels increase significantly in postmenopausal women most likely due to the loss of ovarian sex hormone production [70–72]. The results are in accordance with our baseline comparison, in which women had a higher median Lp(a) concentration than men (p = 0.002). Longitudinal data on premenopausal Lp(a) concentrations were not sufficiently available in our study population.

Secondly, the effect of postmenopausal status on lung function must be taken into consideration. A large study of 141,076 women from the age of 40 to 69 years as well as another cross-sectional analysis of 4,259 women aged 45 to 56 years observed that menopause was associated with lower lung function [73, 74]. Furthermore, menopausal status was associated with more respiratory symptoms and higher prevalence of abnormal lung function compared to premenopausal women [74, 75]. Another longitudinal population-based study observed that decline in lung function was less rapid in women who used hormone replacement therapy (HRT), highlighting the importance of female sex hormones in lung ageing [76].

Thirdly, sex-specific differences in respiratory physiology that are not only due to sex hormones or menopause-induced differences, might also contribute to the discrepancy between the older men and women observed in our study. While the decline of lung function due to age-related changes in the mechanical properties of the lung is physiological (e.g. loss of elastic recoil function), these changes develop later and proceed more slowly in women [77, 78].

These aforementioned effects of postmenopausal status on Lp(a) and lung function as well as the sex-related differences in lung health may at least partly explain why the Lp(a)-lung function association was not as evident in women as in men. However, this could also be a matter of statistical power, since the direction of the associations observed in men and women were quite similar (Fig. 4).

A limitation to our study is that although the longitudinal aspect of this follow-up study was able to confirm the previously observed association between Lp(a) and lung function at baseline, we were unable to establish a causal relationship, as these findings were solely based on an observational approach. As another limitation we need to acknowledge a potential selection bias because only those individuals who participated in both the baseline and follow-up assessments with Lp(a) and spirometry data of sufficient quality available were included for our data analysis. In addition, our study does not reflect the general population as the cohort studied was limited to voluntarily participating residents of the Berlin metropolitan area, aged 60 years and older.

Our study has several strengths that should be acknowledged. The study size was relatively substantial with a total number of 679 participants - greater than the first cross-sectional analysis from BASE-II, as we were able to achieve a higher number of better quality spirometry measurements in the follow-up study. Furthermore, we obtained two separate Lp(a) measurements at baseline and follow-up with a span of 7.4 ± 1.5 years in between, which helped confirm our previous findings through longitudinal as well as cross-sectional analyses. To our knowledge, this is the first longitudinal study that assesses the association between Lp(a) and lung function in older people.

Currently, there is a high interest amongst clinicians and researchers in the development of a pharmacologic therapy that can lower Lp(a) levels in order to reduce the risk for cardiovascular diseases. A phase III trial evaluating an antisense oligonucleotide therapy is currently being awaited with great anticipation [16–20]. However, the observed Lp(a)-lung function association in our study brings to light the potential negative implications of reducing Lp(a) level on lung function over time. Other longitudinal studies and prospective interventional studies with a more diverse age-group on the topic investigated here are needed before a final conclusion on the Lp(a)-lung function association can be drawn. We recommend that future studies take into consideration how biological sex might influence the association between Lp(a) and pulmonary function, as both Lp(a) (mainly for postmenopausal women) and lung function are influenced by sex-linked biological differences [5, 79, 80].

**Conclusion**

In conclusion, we observed that elevated Lp(a) levels were associated with better lung function in older men, and this with a time interval of on average 7.4 years between Lp(a) measurement (baseline) and spirometry (follow-up). Women showed similar findings, but the high Lp(a) and increased lung function association was not statistically apparent. This is suggestive of elevated serum Lp(a) playing an unknown and possibly sex-specific beneficial role in pulmonary health. There are currently no studies that have examined the physiological role of Lp(a) in lung (patho)physiology in general. These large gaps in our understanding of the Lp(a)-lung function relationship open directions for future research.

**Abbreviations**

Lp(a): Lipoprotein(a); CVD: Cardiovascular disease; BASE-II: Berlin Aging Study II; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; MI: Morbidity index; T2D: Type 2 diabetes mellitus; MetS: Metabolic syndrome; SD: Standard deviation; IQR: Interquartile range; ANCOVA: Analysis of covariance; COPD: Chronic obstructive pulmonary disease; GGT: Gamma-glutamyl transferase; ALT: Alanin amino transferase; ALP:
Alkaline phosphatase; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL-C: High-density lipoprotein cholesterol; ApoA-I: Apolipoprotein A1; LDL-C: Low-density lipoprotein cholesterol; ApoB: Apolipoprotein B

Declarations

Availability of data and materials

Due to concerns for participant privacy, data are available only upon reasonable request. Additional information can be obtained from the BASE-II website: https://www.base2.mpg.de/7549/data-documentation. Interested investigators are invited to contact the scientific coordinator of BASE-II, Ludmila Müller (lmueller@mpib-berlin.mpg.de).

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Author contributions

Conceived and designed the study: CKS, NB and ID. Contributed study specific data: VR-Z, ES-T and ID. Analyzed the data: CKS. Methodology: TK, NB and ID. Wrote the original draft: CKS. Supervision: NB and ID. Project administration: ID. All authors revised and approved the manuscript.

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Ethics approval and consent to participate

All participants gave written informed consent and the Ethics Committee of the Charité – Universitätsmedizin Berlin approved the study (approval numbers EA2/029/09 and EA2/144/16).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References


66. Fessler MB. Revisiting “good” and “bad” cholesterol the battle over flow through arteries now shifts to flow through airways. American Journal of Respiratory and Critical Care Medicine; 2015.


Figures
Figure 1

A flow-chart of included and excluded study participants.

A total of 1,164 participants were available in the dataset from the follow-up study, which also included participants who participated in the baseline study. After implementing the exclusion criteria as listed above, 485 participants were excluded, leaving a total 679 participants to be analyzed in the current study.

Figure 2

Paired comparison of lung function measurements at baseline vs. follow-up.
Mean forced expiratory volume in 1 second (FEV1) and mean forced vital capacity (FVC) measured at baseline and follow-up are shown separately for men and women. Both mean FEV1 and FVC measurements have declined after 7.4 years (mean) in both sexes (paired t-test). Men showed higher mean FEV1 and FVC measurements compared to women.

Figure 3

Longitudinal analysis of the association between Lp(a) measured at baseline and lung function measured at follow-up, 7.4 years (mean) later.

Distributions of FEV1 and FVC measurements are compared between participants belonging to Lp(a)-quintile 1 and Lp(a)-quintiles 2-5 separately for men and women. Mean FEV1 and FVC were higher in men categorized in Lp(a)-quintiles 2-5 (t-test). Women in Lp(a)-quintile 2-5 also showed a slightly higher mean FEV1 and FVC than those in Lp(a)-quintile 1.

Figure 4
Estimated means of FEV1 (A and C) and FVC (B and D) at follow-up according to each Lp(a) quintile 1 to 5 from baseline with 95% confidence interval (CI) - adjusted for covariables from baseline.

In both men (A and B) and women (C and D), those categorized in Lp(a)-quintile 3 showed the highest mean FEV1 and FVC measurements. Furthermore, lung function measurements from Lp(a)-quintile 2, 3, 4, and 5 remained consistently higher than those from Lp(a)-quintile 1. In men there were differences in the adjusted means of FEV1 and FVC between Lp(a) quintile 1 vs 2, quintile 1 vs 3, and quintile 1 vs 4 (p<0.05). There was no meaningful difference in the adjusted means of FEV1 and FVC between Lp(a) quintile 1 and 5.

Supplementary Files

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

- SupplementaryMaterial.docx