Dietary factors and lung function in the general population: wine and resveratrol intake

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ABSTRACT

Wine intake is associated with a better lung function in the general population, yet the source of this effect is unknown. Resveratrol, a polyphenol in wine, has anti-inflammatory properties in the lung, effects being partially mediated via induction of Sirtuin 1 (SIRT1) activity. We assessed the impact of wine and resveratrol intake and SIRT1 SNPs on lung function in the general population.

Effects of red and white wine and resveratrol intake on FEV₁, FVC and FEV₁/FVC were analyzed in the population-based Doetinchem cohort (n=3,224). Associations of four tagging SIRT1 SNPs with lung function were analyzed in the Doetinchem (n=1,152) and Vlagtwedde-Vlaardingen (n=1,390) cohorts.

Resveratrol intake was associated with higher FVC levels and white wine intake with higher FEV₁ levels and lower risk of airway obstruction. SIRT1 SNPs were not significantly associated with level or course of lung function, neither directly nor indirectly via wine or resveratrol intake.

This study shows a positive association of resveratrol intake with lung function in the general population, confirms the previously reported positive association of white wine intake with higher levels of FEV₁, and additionally shows an association with a higher FEV₁/FVC ratio. These effects do not likely run via SNPs in SIRT1.

Keywords: lung function; Chronic Obstructive Pulmonary Disease (COPD); wine; Single Nucleotide Polymorphism (SNP); Sirtuin 1 (SIRT1); resveratrol
INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a worldwide prevalent disease with increased mortality and morbidity [1]. An increased inflammatory process with an increased burden of proteases and oxidative stress contribute to progressive airway obstruction and COPD development [2,3]. The known contributors to lung function loss are both of environmental (e.g. smoking) and genetic origin [4-6].

Apart from smoking, other environmental factors are related to the level of lung function, including the consumption of several food compounds e.g. vitamin C [7] and whole grain products [8]. It has also been shown that out of several alcohol sources, only wine intake is positively associated with the level of Forced Expiratory Volume in 1 second (FEV₁) and Forced Vital Capacity (FVC) in the general population [9], but the compound responsible for this effect remains unknown so far. A putative candidate that may account for the observed beneficial effect of wine is resveratrol, a polyphenol present in the skin of grapes. Resveratrol possesses anti-inflammatory properties in airway epithelial cells [10] and in alveolar macrophages derived from COPD patients [11]. The mechanism of this action may be explained by the resveratrol-mediated induction of Sirtuin 1 (SIRT1) activity [12,13]. SIRT1 belongs to the class III histone/protein deacetylases.

The resveratrol-SIRT1 pathway contributes to the lifespan prolongation of several organisms [12,14] and to the improvement of mitochondrial function in mice [15,16]. It has recently been shown that cigarette smoke impairs SIRT1 function in human macrophages in vitro and in rat lungs in vivo, which resulted in an increase of NFκB-
dependent inflammatory burden [13]. Interestingly, this effect was inhibited by resveratrol. Furthermore, the observed post translational modifications of SIRT1 protein by cigarette smoke explained the lower SIRT1 expression in lung tissue of healthy smokers and COPD patients as compared to never smokers [17].

In the current study, performed in the large (n=3,224), prospective population-based Doetinchem cohort, we tried to replicate the previously reported positive association between wine intake and the level of lung function [9]. Furthermore, we calculated the total resveratrol intake and assessed its association with the level and longitudinal decline of lung function that, if abnormally accelerated, can result in the development of COPD [18]. Additionally we studied the role of SIRT1 genetic variations and their interaction with smoking in relation to lung function in two distinct, prospective cohorts i.e. random samples of the Doetinchem and Vlagtwedde-Vlaardingen cohorts in The Netherlands.
METHODS

Subjects

The associations between food compounds and resveratrol intake and lung function were assessed in the Doetinchem cohort study [19], a prospective part of the larger MORGEN study [7]. This Caucasian cohort consists of 3,224 subjects with DNA and spirometry tests available (table 1). We selected a random sub-sample (n=1,152; table E1 in online depository) for DNA analysis as described previously [20]. Between 1994 and 2007 subjects were tested for prebronchodilator lung function (FEV₁ and FVC) three times with 5-year intervals according to the European Respiratory Society (ERS) guidelines [21]. Similarly to the entire Doetinchem cohort, in the random sub-sample 100%, 100% and 70.4% subjects participated in the first, second and third survey respectively. The characteristics of the subjects that were lost to follow-up were not significantly different from those that were examined at the third survey. The Vlagtwedde-Vlaardingen cohort (n=1,390, described previously in detail) [22] was included to replicate genetic findings of the Doetinchem cohort (table E1 in online depository). This Caucasian cohort was prospectively followed for 25 years with lung function measurements every 3 years (see online depository for details on lung function measurements in Doetinchem and Vlagtwedde-Vlaardingen cohorts). In the Vlagtwedde-Vlaardingen cohort, FEV₁ measurements were included from the age of 30 years, because an individual’s maximally attained lung function is assumed to have been reached before that age, and lung function is considered to be either in the plateau or decline phase [22]. In the Doetinchem cohort, all subjects had passed the age of 30 years at the second survey and were thus included in the analysis.
There was no overlap in subjects whatsoever between the two cohorts, due to a
different sampling time frame and sampling from different cities under responsibility
of different institutes. The study protocols were approved by local medical ethics
committees and all participants gave their written informed consent.

**Assessment of the dietary intake in the Doetinchem cohort**

Dietary intake of 178 food items was assessed using a semi-quantitative food
frequency questionnaire filled out by all participants prior to the first and prior to the
second survey in the Doetinchem cohort (n=3,224) [19]. In order to better estimate
the lifetime consumption of these products, the average intake from both surveys
was calculated and used in all analyses. Resveratrol intake was calculated using
previously reported content of resveratrol in 11 food items (table 1) (see online
depository for details) [23-27].

**Genotyping SIRT1**

Four SNPs, that tag all 22 SNPs in SIRT1 and its 5kb up-/downstream region with
$r^2<0.8$ and Minor Allele Frequency$>5\%$ (based on the HapMap release 23a/March
2008), i.e. rs12778366, rs10823108, rs7069102, and rs2273773 were genotyped.
Since SNPs rs10823108 and rs2273773 were in complete linkage disequilibrium
($r^2=1.0$) in both cohorts, only data on rs2273773 are presented. Four haplotypes in
SIRT1 were identified and only one (containing the mutant allele of rs7069102 and
wild type alleles of all the other SNPs) was unique i.e. was not tagged by a single
allele of any investigated SIRT1 SNP (see online depository and table E4 for details).
Statistics

Linear regression was performed to assess associations of the continuously defined average intake of total resveratrol, wine intake, grapes and resveratrol from non-grape products with the level of FEV$_1$ and FVC at the second survey in the Doetinchem cohort (n=3,224, table 1). The average intake of all investigated dietary compounds was log10 transformed to obtain normal distributions (log10(intake+1) for the intake of wine and grapes). Identified significant associations were further analyzed as tertiles and presented in plots.

Logistic regression was used to analyze the associations between the continuously defined average intake of wine and total resveratrol intake and the prevalence of airway obstruction as defined by the Lower Limit of Normal (LLN) FEV$_1$/FVC ratio, LLN FEV$_1$ level, at the second survey (see online depository for the definition of LLN).

Analyses were performed either using SPSS, version 14.0 (regression analyses) or S-PLUS, version 7.0 (LME models). See online depository for details on the statistical analyses. P values<0.05 were considered to be statistically significant (tested 2-sided).
RESULTS

Level of FEV1 and FVC and airway obstruction in relation to wine and resveratrol intake in the Doetinchem cohort (n=3,224)

All subjects consumed resveratrol in any form and red wine was the predominant contributor to the overall resveratrol intake (table 1).

We found no association between red wine intake and level of FEV1 or FVC, or airway obstruction. The intake of white wine was associated with higher FEV1 level, whereas the intake of resveratrol was associated with higher FVC level (figure 1; table E2 online depository).

Since smoking may reduce the anti-inflammatory capacity of SIRT1, an effect inhibited by resveratrol, we further analyzed white wine and resveratrol intake for their interaction with packyears smoked. There was a significant interaction between packyears smoked and white wine intake with the level of FEV1 (p=0.03), and a non-significant one with level of FVC (p=0.07). The interaction reflected that white wine consumption was associated with a higher FEV1 level in heavy smokers only (defined using median of packyears smoked in ever-smokers, figure 2). The interaction term between total resveratrol intake and packyears smoked was not significant with respect to the level of FEV1 (p=0.17) and level of FVC (p=0.27).

White wine intake was significantly associated with a decreased risk for airway obstruction, defined as an FEV1/FVC ratio < LLN level and FEV1 < LLN (table E2 online depository).

Lack of white wine consumption significantly (p=0.017) increased the risk for the combination of FEV1< LLN and FEV1/FVC < LLN, a sign of COPD (figure 3).
FEV₁ decline in relation to wine and resveratrol intake in the Doetinchem cohort (n=3,224)

There was no significant association between the intake of resveratrol, or red or white wine and the change in FEV₁ across the three surveys in the Doetinchem cohort.

Genetic variations in SIRT1 and lung function level and decline in the Doetinchem cohort and Vlagtwedde-Vlaardingen cohort

None of the SIRT1 genetic variations was significantly associated with FEV₁ or FVC level in an additive model (table 3). Additionally, in the pooled cohort none of the SIRT1 variations was associated with FEV₁ level, (F)VVC level, or FEV₁ decline or VC decline analyzed with the recessive or dominant model (data not shown).

Three significant interactions between SIRT1 genetic variations (additive model) and packyears smoked were observed in the Doetinchem cohort and one other in the Vlagtwedde-Vlaardingen cohort in relation to the level of FEV₁ and FVC, but none of these was observed in the pooled cohort analysis (table E4 in the online depository).

We found no significant interaction between SIRT1 variations and resveratrol intake with respect to the FEV₁ or FVC level at the second survey in the random sample of the Doetinchem cohort in any genetic model (see table E5 in the online depository for the additive model).
DISCUSSION

To our knowledge, this is the first study investigating resveratrol intake in relation to level and progressive loss of lung function. We found a positive association of resveratrol intake with FVC level in the general population. Furthermore, we replicate the previously observed positive association of white wine intake with the level of FEV₁ in the general population (9), and extend this observation by showing that white wine intake is positively associated with a lower risk for abnormally low FEV1/FVC ratio, a measure of airway obstruction as present in COPD. Our results do not implicate that heavy wine consumption is protective in any respect. Finally, we conclude that polymorphisms in SIRT1 do not appear to affect lung function neither via an independent association, nor via interaction with packyears smoked or the intake of resveratrol.

Beneficial effects of wine consumption are postulated to account for the “French paradox”, the observation of lower mortality due to coronary heart disease in the French population despite this population’s relatively high consumption of a cholesterol-rich and saturated fat-rich diet [28,29]. The proposed mechanism includes the inhibition of platelet reactivity by wine [28], and resveratrol is a prominent candidate responsible for the vascular protection provided by wine [30]. However, our study shows that white wine intake and not red wine intake, the major dietary resveratrol source, is associated with a lower risk for airway obstruction and with higher FEV₁ levels, both indices of COPD. This is of great importance given the fact that reduced lung function is a marker for cardiovascular related mortality [31].
While we found that resveratrol intake was associated with a higher FVC level, its association with FEV₁ level was not significant. Similarly we did not observe significant associations of resveratrol intake with the presence of airway obstruction. Therefore, the relevance of the observed association in relation to respiratory disorders other than COPD needs to be further addressed. Interestingly, none of the separate grape sources of resveratrol was associated with FVC level and neither was the resveratrol from non-grape sources (data not shown), which suggests that the overall effect of resveratrol intake on FVC is specific and independent of the source (table E2 online depository).

The analysis of individual sources of resveratrol revealed that particularly white wine intake is associated with a higher FEV₁ level. Accordingly, Schünemann and colleagues found white wine to display a stronger effect on FEV₁ level compared with red wine in the cohort of 1,555 New York residents [9]. They suggested that health-promoting lifestyle factors associated with white wine drinking might be responsible for this effect. We like to put forward that other polyphenolic compounds present in white wine may exert beneficial effects on lung function as well. Plausible candidates in this respect are tyrosol and hydroxytyrosol, polyphenolic white wine molecules with, similar to resveratrol, antioxidant and cardioprotective effects in vivo [32]. Other candidates are flavonoids that were associated with a higher level of FEV₁ in the MORGEN study [33]. However since flavonoids like quercetin and myricetin are present in red wine predominantly [34], they are likely not responsible for the positive associations with white wine we found.
We additionally showed that the intake of white wine interacts with the amount of cigarettes smoked. Smokers particularly benefitted from a higher white wine intake. This observation suggests that white wine might be efficient in the detoxification of molecules derived from cigarette smoke that elevate oxidative or inflammatory burden in the lung, and thus the positive associations of white wine intake with lung function become more easily apparent in smokers as compared to never-smokers. Eventually, as shown in our study non-drinkers of white wine are at increased risk for abnormally low FEV$_1$ and low FEV$_1$/FVC levels, both indices of COPD in a moderate stage.

We cannot rule out the possibility that the associations we found between white wine and lung function might be due to confounding, since the habit of drinking white wine might be associated with beneficial characteristics that are actually underlying the relation. However, adjustments for factors we know to be associated with better lung function (e.g. higher socio-economic status and other health beneficial factors) did not substantially change the effect estimates. Reverse causation might be an issue related to this, since people with better health and better lung function might be more affluent and be more likely to drink white wine. Overall, a causal relation between white wine drinking and lung function is not established, and it would be premature to make clinical recommendations based on the current results solely. Additionally, we feel it is important to stress that the positive association we observed between white wine intake and higher FEV$_1$ reflects a very modest average consumption of 1.0-1.5 glass of white wine per week (i.e. 7.4 g/day), and thus by no means aim to suggest that more than moderate white wine drinking could be considered as beneficial health behavior.
We could not include all known dietary intakes of resveratrol i.e. grape juice and fortified wine or other sources suggested to contain resveratrol like hop, present in beer [36] or cherries [37]. Nevertheless, our estimation of resveratrol intake might be acknowledged as sensitive on a population level, since the sources that were not used contain a low concentration of resveratrol [27, 36, 37] and/or are not widely consumed in the total population.

The reproducibility and validity of the used food frequency questionnaire has been well documented in the literature [38, 39]. The reproducibility of alcohol intake and the consumption of alcoholic beverages at 6 and 12 months was high (Spearman’s rank correlation: 0.83-0.94) as was the relative validity against 12 monthly 24-hour recalls (0.74-0.94). Therefore, we expect the reproducibility and relative validity of resveratrol intake and wine consumption to be high as well.

Sensitivity of the current estimation of the resveratrol intake is certainly lower on an individual level. This is due to the fact that the resveratrol content of grapes and wines is affected by many factors that could not be taken into account in the current study. In particular it has been shown that the resveratrol content of wine depends on the type of wine and the region where the grapes were harvested, due to the climate/species dependent resveratrol synthesis by grapes [23, 40, 41].

Since resveratrol induces deacetylase SIRT1 activity in vitro [12-14] and SIRT1 expression is decreased in lung tissue of COPD patients [17], we were interested in analyzing genetic variations in this gene in the context of lung function. Although we found some significant associations of SIRT1 SNPs and their interaction with smoking with lung function level, none of these associations was replicated in the two cohorts investigated. The current study also does not identify any significant
interaction between \textit{SIRT1} SNPs and resveratrol intake with respect to the level of lung function.

In summary, we demonstrate positive association of white wine intake and higher levels of \textit{FEV}_1 in the general population that is pronounced in smokers. Consequently white wine consumption is associated with a lower risk for moderate airway obstruction. We show for the first time that resveratrol intake is associated with higher \textit{FVC} levels on a general population level, which needs further study. Moreover, genetic variants in \textit{SIRT1}, a deacetylase gene that can be induced by resveratrol \textit{in vivo}, are unlikely to play a role in the positive association between resveratrol and lung function.
ACKNOWLEDGEMENTS

The authors thank the epidemiologists and fieldworkers of the Municipal Health Services in Doetinchem for their important contribution to the data collection of the Doetinchem Study as well as Jaap Seidell, Monique Verschuren, Bas Bueno-de Mesquita from the National Institute of Public Health in Bilthoven for conducting the study and Anneke Blokstra and Petra Vissink for the logistic and data management. We thank Jan Schouten for the continuous management of the Vlagtwedde-Vlaardingen data. Last but not least, the authors thank the participants of the Doetinchem and Vlagtwedde-Vlaardingen studies for their loyal participation every survey.

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FIGURE LEGENDS

**Figure 1:** Mean adjusted level of FEV$_1$ and FVC for the subjects according to the average intake of white wine and total resveratrol in the Doetinchem cohort (n=3,224)

Squares represent the adjusted mean and the bars represent 95% confidence interval. White wine intake is depicted according to the intake status and a median intake of 7.4 g/day in white wine consumers. Total resveratrol intake is depicted in tertiles.

FEV$_1$ = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity,
CI=Confidence Interval
Figure 2: Mean adjusted FEV<sub>1</sub> level according to the average intake of white wine and packyears smoked in the Doetinchem cohort (n=3,224)

Squares represent the adjusted mean and the bars represent 95% Confidence Interval (CI). White wine intake is depicted according to the intake status and a
median intake of 7.4 g/day in white wine consumers. Mild/heavy smokers are depicted according to the median of packyears smoked in ever-smokers (e.g. 13.0 packyears).

\[
\text{FEV}_1 = \text{Forced Expiratory Volume in 1 second}
\]

**Figure 3:** Adjusted relative risks for a low FEV\(_1\)/FVC ratio and normal FEV\(_1\) level, and for a low FEV\(_1\)/FVC ratio and low FEV\(_1\) level according to the intake of white wine. Squares represent the relative risks and the bars represent 95% confidence intervals.

The reference group (n=2,290) has FEV\(_1\)/FVC ≥ LLN and FEV\(_1\) ≥ LLN and no respiratory symptoms (breathlessness, chronic cough and chronic phlegm.
production). Numbers correspond to subjects identified within each group in the Doetinchem cohort.

FEV$_1$ = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; LLN = Lower Limit of Normal
**Table 1**: Characteristics of the total Doetinchem cohort (n=3,224) at the second survey

<table>
<thead>
<tr>
<th>Time of the visit</th>
<th>1999-2002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males, n (%)</strong></td>
<td>1560 (48.4%)</td>
</tr>
<tr>
<td><strong>Age in years, median (range)</strong></td>
<td>50.0 (31.2-70.9)</td>
</tr>
<tr>
<td><strong>Height in cm, mean (SD)</strong></td>
<td>172.8 (9.2)</td>
</tr>
<tr>
<td><strong>Smokers/Ex-smokers, n (%)</strong></td>
<td>859 (26.7) / 1259 (39.1)</td>
</tr>
<tr>
<td><strong>Packyears smoked, median (range):</strong></td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td>4.6 (0.0-154.0)</td>
</tr>
<tr>
<td>Ever-smokers</td>
<td>13.0 (0.004-154.0)</td>
</tr>
<tr>
<td><strong>FEV₁ in liters, mean (SD)</strong></td>
<td>3.41 (0.80)</td>
</tr>
<tr>
<td><strong>FVC in liters, mean (SD)</strong></td>
<td>4.38 (1.02)</td>
</tr>
<tr>
<td><em><em>FEV₁ change in ml/year</em>, mean (SD)</em>*</td>
<td>-26.03 (34.07)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The average intake of:</th>
<th>% of consumers in the population</th>
<th>median (IQR) in consumers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wine [g/day]</td>
<td>76.2</td>
<td>23.3 (7.1-67.6)</td>
</tr>
<tr>
<td>White wine [g/day]</td>
<td>65.1</td>
<td>7.4 (2.5-21.4)</td>
</tr>
<tr>
<td>Red wine [g/day]</td>
<td>65.4</td>
<td>15.4 (3.3-50.0)</td>
</tr>
<tr>
<td>Grapes [g/day]</td>
<td>99.4</td>
<td>8.1 (4.3-13.9)</td>
</tr>
<tr>
<td>Resveratrol [μg/day]</td>
<td>100.0</td>
<td>122.9 (36.0-506.2)</td>
</tr>
<tr>
<td>Resveratrol from non-grape products [μg/day]†</td>
<td>100.0</td>
<td>8.0 (5.6-11.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Food item, % contribution to the resveratrol intake (resveratrol concentration in mg/100g)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Red wine</td>
<td>84.1 (1.43)</td>
</tr>
<tr>
<td>White wine</td>
<td>9.5 (0.33)</td>
</tr>
<tr>
<td>Grapes</td>
<td>4.3 (0.20)</td>
</tr>
<tr>
<td>Raw tomatoes</td>
<td>0.6 (0.06)</td>
</tr>
<tr>
<td>Peanut butter</td>
<td>0.4 (0.07)</td>
</tr>
<tr>
<td>Chocolate</td>
<td>0.3 (0.05)</td>
</tr>
<tr>
<td>Strawberries</td>
<td>0.2 (0.02)</td>
</tr>
<tr>
<td>Chocolate bars</td>
<td>0.2 (0.02)</td>
</tr>
<tr>
<td>Peanuts</td>
<td>0.1 (0.01)</td>
</tr>
<tr>
<td>Peanut sauce</td>
<td>0.1 (0.04)</td>
</tr>
<tr>
<td>Chocolate milk</td>
<td>0.1 (0.002)</td>
</tr>
</tbody>
</table>

*calculated with the last and the first available FEV₁ measurement

†includes the resveratrol intake derived from tomatoes, strawberries, cocoa-containing and peanut-containing food items

FEV₁ = Forced Expiratory Volume in 1 second
FVC = Forced Vital Capacity
SD = Standard Deviation
IQR = Interquartile Range
Table 2: *SIRT1* genotype characteristics in the two cohorts studied

<table>
<thead>
<tr>
<th>Total <em>SIRT1</em> SNP call rate, (%)</th>
<th>Doetinchem cohort (n=1,152)</th>
<th>Vlagtwedde-Vlaardingen cohort (n=1,390)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heterozygotes n (%)</td>
<td>Homozygotes mutant n (%)</td>
</tr>
<tr>
<td>rs12778366†</td>
<td>264 (23.2)</td>
<td>27 (2.4)</td>
</tr>
<tr>
<td>rs7069102‡</td>
<td>529 (46.9)</td>
<td>145 (12.8)</td>
</tr>
<tr>
<td>rs2273773§</td>
<td>173 (15.3)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Unique haplotype</td>
<td>276 (24.4)</td>
<td>15 (1.3)</td>
</tr>
</tbody>
</table>

* for 1 df chi-square test comparing the observed genotypes distribution with the expected as derived from the allele frequencies

† located in the *SIRT1* promoter; tagged SNP located in the intron 3

‡ located in the *SIRT1* intron 4; tagged SNPs located in the promoter, introns 1 – 8 and 3’ near region

§ synonymous SNP (Leu332Leu) in the exon 5; tagged SNPs located in the promoter and introns 3 - 5

SNP = Single Nucleotide Polymorphism; df = degree of freedom; HWE = Hardy-Weinberg Equilibrium; MAF = Minor Allele Frequency; *SIRT1* = Sirtuin 1
**Table 3:** Estimated effects of the *SIRT1* genetic variation (additive model) on lung function parameters in the random sample of the Doetinchem cohort and Vlagtwedde-Vlaardingen cohort

<table>
<thead>
<tr>
<th><em>SIRT1</em> genetic variation:</th>
<th>Doetinchem (n=1,152)</th>
<th>Vlagtwedde-Vlaardingen (n=1,390)</th>
<th>Pooled cohorts (n=2,542)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>rs12778366</td>
<td>23.7</td>
<td>27.8</td>
<td>0.39</td>
</tr>
<tr>
<td>rs7069102</td>
<td>17.8</td>
<td>18.6</td>
<td>0.34</td>
</tr>
<tr>
<td>rs2273773</td>
<td>-1.5</td>
<td>32.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Unique haplotype</td>
<td>-4.2</td>
<td>29.6</td>
<td>0.89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VC level [ml]*</th>
<th>B</th>
<th>SE</th>
<th>p</th>
<th>B</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12778366</td>
<td>49.8</td>
<td>30.9</td>
<td>0.11</td>
<td>19.5</td>
<td>32.5</td>
<td>0.55</td>
</tr>
<tr>
<td>rs7069102</td>
<td>36.3</td>
<td>20.7</td>
<td>0.08</td>
<td>-10.8</td>
<td>24.1</td>
<td>0.66</td>
</tr>
<tr>
<td>rs2273773</td>
<td>-17.9</td>
<td>35.7</td>
<td>0.62</td>
<td>-42.7</td>
<td>41.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Unique haplotype</td>
<td>-9.4</td>
<td>34.5</td>
<td>0.79</td>
<td>29.6</td>
<td>28.8</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; change [ml/year]†</th>
<th>B</th>
<th>SE</th>
<th>p</th>
<th>B</th>
<th>SE</th>
<th>p</th>
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<td>0.25</td>
<td>0.5</td>
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<td>rs2273773</td>
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<td>2.6</td>
<td>0.053</td>
<td>0.2</td>
<td>1.7</td>
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<td>Unique haplotype</td>
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<td>0.69</td>
<td>2.0</td>
<td>1.4</td>
<td>0.18</td>
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</table>

*linear regression analysis adjusted for sex, age, packyears smoked and height and the cohort binary variable for the pooled analysis

†Linear Mixed Effect model analysis adjusted for the age at entry, sex, initial FEV<sub>1</sub> level (cohort binary variable for the pooled analysis) and their interaction with time

FEV<sub>1</sub> = Forced Expiratory Volume in 1 second
VC = Vital Capacity measured as Forced VC in the Doetinchem cohort and Inspiratory VC in the Vlagtwedde-Vlaardingen cohort
*SIRT1* = Sirtuin 1