www.AUSTRALIANACADEMICPRESS.com.au

ARTICLE AVAILABLE ONLINE
Twin Research and Human Genetics
Volume 14 ▮ Number 5 ▮ pp. 401–407

Heritability of Lung Function: A Twin Study Among Never-Smoking Elderly Women

Maria Hukkinen,[1,2] Jaakko Kaprio,[1,2,3] Ulla Broms,[1,2] Anne Viljanen,[4] Daniel Kotz,[5] Taina Rantanen[4] and Tellervo Korhonen[1,2]

[1] *Department of Public Health, Hjelt Institute, University of Helsinki, Finland*
[2] *National Institute for Health and Welfare, Helsinki, Finland*
[3] *Institute of Molecular Medicine, University of Helsinki, Finland*
[4] *The Gerontology Research Center, Department of Health Sciences, University of Jyväskylä, Finland*
[5] *Department of General Practice, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre, the Netherlands*

Most studies on lung function heritability have been conducted in smokers and non-smokers using cross-sectional study design. Smoking patterns may, however, confound the contribution of genetic factors. We investigated heritability of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio longitudinally, excluding the effects of smoking. A sample of never smoking female twins (n = 374), aged 63–76 at baseline, answered health questionnaires and attended spirometry in years 2000 and 2003. Bivariate structural equation modeling, restricted to adequate spirometry performances (baseline n = 339, follow-up n = 252), was used to estimate genetic and environmental influences on consecutive measurements of FEV1, FVC, and FEV1/FVC. The best-fitting models included additive genetic and non-shared environmental effects. Heritability estimates of 32% and 36% for FEV1, 41% and 37% for FVC, while 46% and 16% for FEV1/FVC were found at baseline and at follow-up. Genetic correlation between FEV1 and FEV1/FVC heritability estimates approached unity, whereas correlation between FVC estimates was 0.80. Environmental correlations were 0.69 for FEV1, 0.62 for FVC, and 0.07 for FEV1/FVC. In never smokers, additive genetic and non-shared environmental effects explain the inter-individual variations in FEV1, FVC, and FEV1/FVC. One third of the variation in FEV1 and FVC is explained by genetic and two thirds by environmental effects. Between 2000 and 2003, environmental effects on FEV1/FVC changed, and the proportion of variance explained by environmental effects increased remarkably. Genetic effects on FEV1 and FEV1/FVC are common to consecutive measurements, whereas at follow-up, new genetic factors explained 14% of the observed variance in FVC.

■ **Keywords:** heritability, lung function, twin study

Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and the ratio of FEV1/FVC comprise the most important lung function measures. After having reached maximal levels in early adulthood, they begin to decrease (Kohansal et al., 2009). Height and physical activity are associated with higher spirometric values (Amara et al., 2001). Age- and height-corrected lung volumes and maximal expiratory flow rates are lower in women than in men (Kohansal et al., 2009; Viljanen, 1982).

Environmental factors during both lung development and adulthood affect lung function. Childhood and in utero factors may impair achievement of maximal lung function (Bakke, 2003). Later in life, passive and active smoking, occupational dusts, air pollution, obesity, sedentary lifestyle, and inflammatory diseases may speed up the age-related decline (Amara et al., 2001; Steele et al., 2009; Stern et al., 2007; Wilk et al., 2000). Environmental exposure can affect lungs also through gene-environment (GxE) interaction (Hallberg et al., 2010; Wilk et al., 2000; Zhai et al., 2007). Poor lung function is associated with cardiovascular, metabolic, and respiratory morbidity (Kohansal et al., 2009; Steele et al., 2009).

Heritability estimates vary as a function of environmental effects and population characteristics. Previously

RECEIVED 21 March, 2011; ACCEPTED 14 April, 2011.

ADDRESS FOR CORRESPONDENCE: Maria Hukkinen, Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland. Email: maria.hukkinen@helsinki.fi

estimated multivariate-adjusted heritabilities are 40%–65% for FEV1, 40%–55% for FVC, and 45% for FEV1/FVC ratio (Hallberg et al., 2010; McClearn et al., 1994; Palmer et al., 2001; Wilk et al., 2000). Genome-wide association (GWA) studies have identified multiple single-nucleotide polymorphisms (SNPs) associated with lung function (Hancock et al., 2010; Repapi et al., 2010). However, these SNPs account only for < 1% of the variance in the traits, and most genetic factors related to lung function variance remain unidentified.

Genetics affects both smoking and body composition (Ordonana et al., 2007; Vink et al., 2005), and together with age, they comprise the main factors modifying lung function heritability (Amara et al., 2001; Hallberg et al., 2010; Wilk et al., 2000). Previous studies on lung function heritability are cross-sectional and include smokers and non-smokers. Moreover, some lack adjustment for smoking and body size. Our objective was to determine the heritability of FEV1, FVC, and the ratio of FEV1/FVC among never smokers, which also eliminates the possible smoking-gene-interaction. The second objective was to study to what extent the heritability estimates correlated longitudinally.

Materials and Methods

Participants

This work is a part of the Finnish Twin Study on Aging (FITSA), examining the contribution of genetic and environmental influences on the disablement process in older women. The study design and recruitment is described in detail elsewhere (Tiainen et al., 2009). FITSA participants were recruited from the Finnish Twin Cohort comprising all same-sex twin pairs born before 1958 and alive in 1975 (Kaprio & Koskenvuo, 2002). A subset of 414 female twin pairs, having participated in 1975, were contacted again in 2000. Inclusion criteria were the willingness of both sisters to participate and the ability to travel to the laboratory. After exclusion of pairs with one or both sisters refusing to participate, having poor health status or being deceased, the sample consisted of 217 pairs aged 63–76. At follow-up

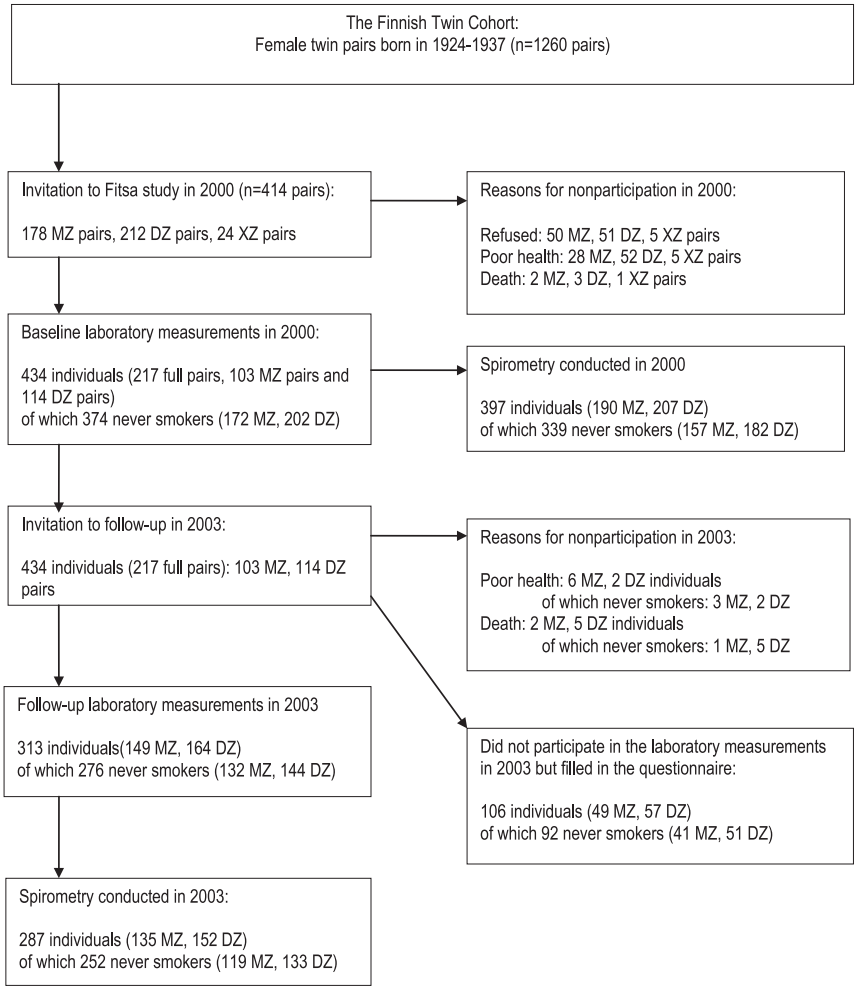

FIGURE 1

Recruitment of the participants. MZ, monozygotic; DZ, dizygotic; XZ, undetermined zygosity; FITSA, Finnish Twin Study on Aging.

https://doi.org/10.1375/twin.14.5.401 Published online by Cambridge University Press

3 years later, individual twins could participate even if their co-twins refused. The attendance of subjects is described in Figure 1.

Smoking behavior and health status were assessed with a questionnaire completed before the laboratory visit and checked during an interview before the clinical examination. The zygosity of the twins was confirmed with DNA extracted from blood samples. A physician ascertained the disease status. Body mass index (BMI) was calculated as a function of measured weight and height (kg/m^2). Laboratory measurements, including spirometry, were conducted after the clinical examination.

In 2003, all participants were invited to a follow-up examination. The questionnaire was completed by 98% (n = 368) of never smokers, whereas 74% (n = 276) participated also in laboratory measurements (Fig 1), conducted similarly as at baseline. Among the whole sample, the attendance rates were slightly lower: 97% (n = 419) and 72% (n = 313). Poor health and difficulties to travel to the laboratory were the most common reasons for non-attendance in the clinical study.

The FITSA study was approved by the Ethics Committee of the Central Finland Health Care District. All participants gave their written informed consent prior to the study.

Dependent Variables

Lung function measures were derived from spirometry and analyzed as continuous variables. At baseline, 339 never smokers provided sufficient spirometry data, including all values except post-bronchodilator tests. Measurements were conducted according to international guidelines (American Thoracic Society, 1995) using an electronic spirometer (Spiro 2000, Medikro Oy). Reasons for non-attendance in spirometry (n = 25) were lack of time, doctor's opinion, and communication problems. In addition, 10 subjects provided incomplete performances. At follow-up, 276 never smokers underwent spirometry, of which one performance was incomplete and therefore excluded. Reasons for non-attendance (n = 23) were lack of time, doctor's opinion, falling ill and computer malfunction.

Other Variables

Overall lung health was defined by asking whether one suffered from chronic cough or sputum production (baseline), had a diagnosis of chronic bronchitis, chronic or seasonal asthma, emphysema, or other pulmonary diseases, such as tuberculosis, alveolitis, bronchitis, pneumothorax, pneumonia, embolus, sarcoidosis, pleuritis, fibrosis, allergy, or chronic obstructive pulmonary disease (baseline and follow-up). For baseline and follow-up, we created dichotomous variables describing lung health; coded 1 if suffering from any of these disorders.

Self-reported leisure time physical activity was categorized as sedentary (no other activity but light walking two or fewer times a week), moderate activity (walking or other light exercise at least three times a week, but no exercise more intensive than that), and high activity (moderate or vigorous activity at least three times per week) (Schroll, 2003).

Subjects who reported not being current smokers, and answered negatively to the question 'Have you ever smoked more than 5–10 packs of cigarettes?' were defined as never smokers. Majority (86.4%) of the participants were never smokers.

Statistical Methods

Based on literature (Kohansal et al., 2009; Mannino & Davis, 2006; Wilk et al., 2000; Zhai et al., 2007), height, weight, BMI, physical activity, lung health and occupation were considered as potential confounders. In order to define covariates for genetic modeling, confounding effects were assessed with linear regressions and saturated genetic models. Adjustment for age centred to its mean value was used in all analyses, resulting in informative intercepts in linear regression equations.

Phenotypic correlations between FEV1, FVC, and FEV1/FVC were used as the basis of genetic modeling. Intraclass correlation coefficients (ICC) were computed for monozygotic (MZ) and dizygotic (DZ) twin pairs to estimate within-pair similarity. Greater similarity between MZ than DZ twin pairs is suggestive for genetic influence on the trait. Cross-twin, cross-time correlations between baseline spirometry measures in one twin and follow-up measures in the co-twin were computed for MZ and DZ twin pairs to explore shared genetic influences in explaining the covariance in the trait longitudinally. Heritability is defined as the proportion of total variance due to genetic effects, assuming that the phenotypic variance can be decomposed into additive genetic (A), dominant genetic (D) or shared environmental (C), and non-shared environmental (E) factors. MZ and DZ twins are assumed to be equally susceptible to environmental influences. MZ twins share all, while DZ twins share on average 50% of their segregating genes. The expected correlations for A, D and C between the twins of a MZ pair are 1.0, while for DZ pairs, the correlations are 0.5 for A, 0.25 for D, and 1.0 for C. E effects are uncorrelated in both MZ and DZ twins. E also includes random effects being therefore always included in the models. Based on these expectations, different models (ACE, ADE, AE, CE and E) were fitted to the data, the aim being to obtain the most parsimonious and best-fitting model to explain the observed pattern of similarity in MZ and DZ pairs (Boomsma et al., 2002).

First, we tested general assumptions and covariates with saturated models. Then, univariate ACE and ADE models were run for FEV1, FVC and FEV1/FVC. Full ACE and ADE models were modified by dropping the least significant parameter at a time. We used likelihood ratio tests and Akaike's information criterion (AIC) to compare alternative models (ACE vs. ADE), whereas χ^2- and p

https://doi.org/10.1375/twin.14.5.401 Published online by Cambridge University Press

values when comparing submodels to the more saturated ones (Neale & Maes, 2006).

To evaluate whether genetic effects are shared by repeated measurements or whether they are measurement point specific, we used a bivariate Cholesky decomposition (Posthuma et al., 2003). In such an ACE or ADE model, effects A_1, C_1, D_1 and E_1 are common to baseline and follow-up, while A_2, C_2, D_2 and E_2 load only on the later measurement point. Heritability estimate of the phenotype is the fraction of genetic variance from the total variance. Variances are derived by squaring the path (standard) coefficients *x*, *y* and *z* of the latent variables A, D or C, and E. The phenotypic variance for the trait thus equals $x^2 + y^2 + z^2$ (Boomsma et al., 2002).

Linear regression models and correlations were calculated with Stata statistical software (StataCorp, 2009), which allows taking into account that the sampling unit has been a twin pair rather than an individual. Uni- and multivariate structural equation modeling was implemented in Mx software and based on standard Mx scripts obtained from the GenomEUtwin Mx website (http://www.psy.vu.nl/mxbib/).

Results

Characteristics

Mean age at baseline was 68.7 years. Mean FEV1 values were 2.23 (*SD* 0.48) in 2000 and 2.18 (*SD* 0.45) in 2003, and mean FVC values were 2.84 (*SD* 0.60) and 2.74 (*SD* 0.57), respectively. The mean FEV1/FVC values were lower (74.4%, SD 8.93) and 77.38, *SD* 7.11), whereas the mean FEV1 and FVC values were higher than the age and height corrected reference values (Viljanen, 1982).

Lifetime pulmonary disease prevalence (lung health coded 1) was 20% (baseline $n = 74$, follow-up $n = 56$). Over half of these suffered from asthma (baseline $n = 44$, follow-up $n = 36$). Chronic bronchitis was the second most common lung disease (baseline $n = 10$, follow-up $n = 6$), whereas other pulmonary diseases were reported by 0–5 subjects. Only 4.3% of the study subjects were classified as sedentary, whereas 62% reported moderate and 34% high physical activity.

TABLE 1

Interclass Correlation Coefficients (with 95% Confidence Intervals) for Forced Expiratory Volume in One Second (FEV1) and Forced Vital Capacity (FVC) in Monozygotic and Dizygotic Never-Smoking Twin Pairs at Baseline (2000) and at Follow-Up (2003)

Correlation	MZ	DZ
FEV1 2000	0.73 (0.60, 0.83)	0.20 (-0.03, 0.41)
FEV1 2003	0.49 (0.23, 0.69)	0.29 (0.01, 0.53)
FVC 2000	0.71 (0.56, 0.81)	0.25 (0.03, 0.45)
FVC 2003	0.44 (0.17, 0.65)	0.36 (0.09, 0.58)

Lung Function Associations

Linear regression models at baseline showed significant associations between FEV1, FVC and BMI ($p \leq .001$), height ($p \leq .001$), lung health ($p = .001$ for FEV1, $p = .049$ for FVC), and physical activity ($p \leq .001$). Follow-up associations were similar. No significant associations between FEV1/FVC ratio and height or BMI were observed, although height association at follow-up was close to the significance level ($p = .057$). FEV1/FVC was significantly associated with lung health and physical activity at both time points (all *p* values < .03).

Pairwise Correlations

ICCs were greater for MZ than for DZ twin pairs (Table 1), indicating that genetics probably explain a significant proportion of the variance in lung function measures. Only the ICCs for FEV1/FVC ratio did not differ between MZ and DZ pairs at follow-up. Cross-twin, cross-time correlations further emphasize the importance of genetics. For example, the correlation of baseline FEV1 of twin 1 with follow-up FEV1 of twin 2 was 0.59 among MZ twins, while 0.28 among DZ twins, suggesting that genetic influences shared by both time points exist for FEV1 (Table 2, only results for FEV1 are shown).

Genetic Modeling

Alternative covariate combinations were tested with saturated models. For FEV1, the best-fitting model was adjusted for age, BMI, physical activity and lung health, covariates explaining 21% of the observed variance at

TABLE 2

Correlations Between FEV1 in 2000 and in 2003 in Monozygotic and Dizygotic Never-Smoking Twin Pairs

	Twin 1		Twin 2	
	FEV1 in 2000	FEV1 in 2003	FEV1 in 2000	FEV1 in 2003
Twin 1				
FEV1 in 2000	—	**0.89**	**0.74**	**0.59**
FEV1 in 2003	*0.75*	—	**0.64**	**0.49**
Twin 2				
FEV1 in 2000	*0.20*	*0.14*	—	**0.87**
FEV1 in 2003	*0.28*	*0.29*	*0.78*	—

Note: Correlations for MZ pairs are in bold; those for DZ pairs in italics.

https://doi.org/10.1375/twin.14.5.401 Published online by Cambridge University Press

baseline and 20% at follow-up. Respectively, covariates used for FVC were age, BMI and physical activity, explaining 15% of the variance at both measurements. For FEV1/FVC, the best-fitting model was adjusted for age, height, lung health, and physical activity, which explained 7% and 8% of the observed variance.

Bivariate Cholesky decompositions included 344 observations for FVC and 339 for FEV1 and FEV1/FVC, allowing missing data at follow-up. Full Cholesky models were reduced to obtain best-fitting models, which were AE models for each variable. For FEV1 (Figure 2), the additive genetic factors in common for both measurements explained 32% (95% CI 7.8–56) of the variance at baseline, and 36% (95% CI 12–56) at follow-up. The genetic correlation approached unity, indicating no genetic innovations specific for the follow-up measurement. Respectively, non-shared environmental effects accounted for 68% (95% CI 44–92) of the variance at baseline and 64% (95% CI 44–88) at follow-up. The environmental correlation between baseline and follow-up was 0.69 (95% CI 0.56–0.80).

In the final Cholesky model for FVC (Figure 3), the genetic effects accounted for 41% (95% CI 13–63) of the variation at baseline and 37% (95% CI 12–57) at follow-up. The genetic correlation between baseline and follow-up was 0.80 (95% CI 0.44–1.00), and 14% of the variance at follow-up was explained by new genetic effects. Non-shared environmental effects explained 59% (95% CI 37–87) of the variance at baseline and 63% (95% CI 43–88) at follow-up. The environmental correlation between baseline and follow-up was 0.62 (95% CI 0.41–0.77).

For FEV1/FVC ratio, genetic effects in the final model explained 46% (95% CI 17–68) of the variance at baseline and 16% (95% CI 0.2–40) at follow-up, genetic correlation approaching unity (Figure 4). Environmental correlation was 0.07 (95% CI–0.18-0.37). At follow-up, < .1% of the variance was explained by environmental effects common to baseline.

Discussion

Among never smoking elderly women, heritability estimates of 32% and 36% for FEV1, 41% and 37% for FVC, and 46% and 16% for FEV1/FVC were achieved at baseline and at follow-up. Results denote that spirometry measures are multifactorial phenotypes, where the inter-individual variation is largely explained by environmental effects. For FEV1 and FEV1/FVC, the additive genetic effects explaining rest of the variation remained the same over follow-up. For FVC, genetic innovations explained 14% of the variance at follow-up. Environmental effects on FEV1/FVC were different at baseline and at follow-up, suggesting that time-specific environmental factors strongly affect FEV1/FVC.

Previously reported lung function heritability estimates in different study populations are higher (Hallberg et al.,

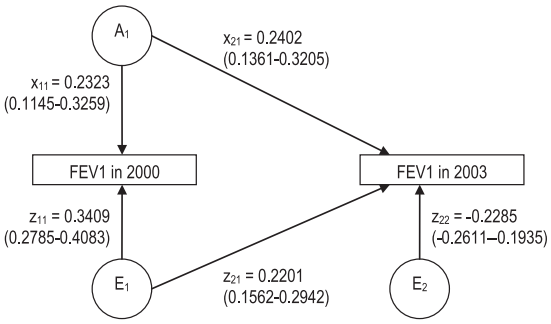

FIGURE 2

The most parsimonious Cholesky decomposition model for FEV1 at baseline in 2000 and at follow-up in 2003. The model consists of additive genetic effect A1 and nonshared environmental effect E1 in common for both measurement points. In addition, FEV1 measured in 2003 has its own nonshared environmental effect E2. The coefficients shown are standardized parameter estimates with 95% confidence intervals of the genetic and environmental latent factors.

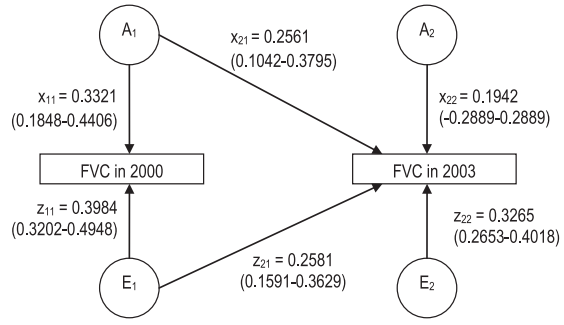

FIGURE 3

The most parsimonious Cholesky decomposition model for FVC at baseline in 2000 and at follow-up in 2003. The model consists of additive genetic effect A1 and nonshared environmental effect E1 in common for both measurement points. In addition, FVC measured in 2003 has its own additive genetic effect A2 and nonshared environmental effect E2. The coefficients shown are standardized parameter estimates with 95% Confidence Interval of the genetic and environmental latent factors.

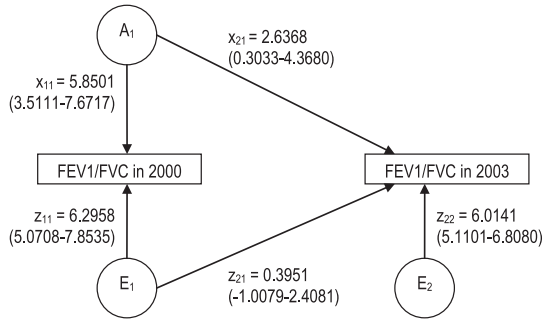

FIGURE 4

The most parsimonious Cholesky decomposition model for FEV1/FVC ratio at baseline in 2000 and at follow-up in 2003. The model consists of additive genetic effect A1 and nonshared environmental effects E1 and E2. A1 is common for both measurement points, but E1 mainly loads on the baseline measurement. At follow-up, 99.6% of the environmental effects are explained by E2. The coefficients shown are standardized parameter estimates with 95% confidence intervals of the genetic and environmental latent factors.

https://doi.org/10.1375/twin.14.5.401 Published online by Cambridge University Press

2010; McClearn et al., 1994; Palmer et al., 2001; Wilk et al., 2000). However, this is the first study where lung function heritability is examined longitudinally in elderly never smokers. By excluding the effect of smoking, we could also control for smoking-gene interaction. Our finding that never smokers' genetic expression of FVC is modified in time suggests that other environmental factors than smoking also influence lung function genes. Such changeability in gene expression complicates definition and interpretation of specific lung function loci.

Strengths of this study include exclusion of the smoking effect, extensive consideration of potential confounders, and longitudinal study design. Repeated measurements validated our results and allowed us to decompose the observed variance into time specific genetic and environmental effects. Estimating genetic and environmental correlations in time would not be possible if the outcome was measured only in only one time point.

Our results cannot be applied to men or younger women. However, excluding smoking effect in elderly males would be more complicated because smoking prevalence is higher. In a Swedish sample, no gender differences existed in FEV1 and FVC heritability. However, age differences were found (McClearn et al., 1994), suggesting that contributions of A and E effects would also differ between younger women and our study subjects. Further, environmental factors affecting pulmonary function vary with age. Structural changes in lungs and chest wall, and disease processes such as vertebrae fractures, are typical in the elderly (Sharma & Goodwin, 2006). For FEV1/FVC ratio, we observed substantial changes in the proportions of genetic and environmental effects in time, which may also be explained by such environmental factors.

Our study subjects were possibly healthier than women generally in this age group. Traveling ability was an inclusion criterion, so subjects with severe health problems were excluded. For example, when compared nationally to women aged 65–74 years (Sulander et al., 2001), never smoking FITSA participants were physically more active and their self-perceived functional capacity was better. Among them, prevalences of coronary artery disease (12%), hypertension (38%), and type 2 diabetes (6.2%) were also lower than in the national sample.

This analysis has certain limitations. Non-attendance in spirometry and study drop-outs could have affected the results. The mean lung function measures at baseline were poorer in those who dropped out (FEV1 2.10, FVC 2.69, FEV1/FVC 73.2%) than in the whole sample. Unfortunately, passive smoking and occupational exposure, which are important lung function predictors, were not assessed. Further, smoking, physical activity, and disease status were all self-reported and not objectively validated, which may have caused some misclassification.

Impaired lung function increases the risk of pulmonary disorders, metabolic syndrome, osteoporosis, cardiovascular diseases, and premature death (Kohansal et al., 2009; Steele et al., 2009). Unique environmental factors, others than smoking, explain the majority of lung function variation in never-smoking elderly women. Screening and prevention of known environmental risk factors could result in better lung function, overall health, and reduced mortality in the old age.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

The analyses and writing of this article was supported by funding of the Yrjö Jahnsson Foundation (TK and MH). The Finnish Twin Study on Aging was funded by the Ministry of Education, the Academy of Finland, and the GENOMEUTWIN project. The Finnish Twin Cohort study is funded by the Academy of Finland Centre of Excellence in Complex Disease Genetics.

References

Amara, C. E., Koval, J. J., Paterson, D. H., & Cunningham, D. A. (2001). Lung function in older humans: The contribution of body composition, physical activity and smoking. *Annals of Human Biology, 28*, 522–536.

Bakke, P. S. (2003). Factors affecting growth of FEV1. *Monaldi Archives for Chest Disease, 59*, 103–107.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3*, 872–882.

Hallberg, J., Iliadou, A., Anderson, M., de Verdier, M. G., Nihlen, U., Dahlback, M., Pedersen, N. L., Higenbottam, T., & Svartengren, M. (2010). Genetic and environmental influence on lung function impairment in Swedish twins. *Respiratory Research, 11*, 92.

Hancock, D. B., Eijgelsheim, M., Wilk, J. B., Gharib, S. A., Loehr, L. R., Marciante, K. D., Franceschini, N., van Durme, Y. M., Chen, T. H., Barr, R. G., Schabath, M. B., Couper, D. J., Brusselle, G. G., Psaty, B. M., van Duijn, C. M., Rotter, J. I., Uitterlinden, A. G., Hofman, A., Punjabi, N. M., Rivadeneira, F., Morrison, A. C., Enright, P. L., North, K. E., Heckbert, S. R., Lumley, T., Stricker, B. H., O'Connor, G. T., & London S. J. (2010). Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nature Genetics, 42*, 45–52.

Kaprio, J., & Koskenvuo, M. (2002). Genetic and environmental factors in complex diseases: The older finnish twin cohort. *Twin Research, 5*, 358–365.

Kohansal, R., Martinez-Camblor, P., Agusti, A., Buist, A. S., Mannino, D. M., & Soriano, J. B. (2009). The natural history of chronic airflow obstruction revisited: An analysis of the framingham offspring cohort. *American Journal of Respiratory and Critical Care Medicine, 180*, 3–10.

Mannino, D. M., & Davis, K. J. (2006). Lung function decline and outcomes in an elderly population. *Thorax, 61*, 472–477.

McClearn, G. E., Svartengren, M., Pedersen, N. L., Heller, D. A., & Plomin, R. (1994). Genetic and environmental influences on pulmonary function in aging Swedish twins. *Journal of Gerontology, 49*, 264–268.

Neale, M. C., & Maes, H. H. M. (2006). *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic Publishers B.V.

Ordonana, J. R., Rebollo-Mesa, I., Gonzalez-Javier, F., Perez-Riquelme, F., Martinez-Selva, J. M., Willemsen, G., & Boomsma, D. I. (2007). Heritability of body mass index: A comparison between the Netherlands and Spain. *Twin Research & Human Genetics, 10*, 749–756.

Palmer, L. J., Knuiman, M. W., Divitini, M. L., Burton, P. R., James, A. L., Bartholomew, H. C., Ryan, G., & Musk, A. W. (2001). Familial aggregation and heritability of adult lung function: Results from the Busselton health study. *European Respiratory Journal, 17*, 696–702.

Posthuma, D., Beem, A. L., de Geus, E. J., van Baal, G. C., von Hjelmborg, J. B., Iachine, I., & Boomsma, D. I. (2003). Theory and practice in quantitative genetics. *Twin Research, 6*, 361–376.

Repapi, E., Sayers, I., Wain, L. V., Burton, P. R., Johnson, T., Obeidat, M., Zhao, J. H., Ramasamy, A., Zhai, G., Vitart, V., Huffman, J. E., Igl, W., Albrecht, E., Deloukas, P., Henderson, J., Granell, R., McArdle, W. L., Rudnicka, A. R., Wellcome Trust Case Control Consortium, Barroso, I., Loos, R. J., Wareham, N. J., Mustelin, L., Rantanen, T., Surakka, I., Imboden, M., Wichmann, H. E., Grkovic, I., Jankovic, S., Zgaga, L., Hartikainen, A. L., Peltonen, L., Gyllensten, U., Johansson, A., Zaboli, G., Campbell, H., Wild, S. H., Wilson, J. F., Glaser, S., Homuth, G., Volzke, H., Mangino, M., Soranzo, N., Spector, T. D., Polasek, O., Rudan, I., Wright, A. F., Heliövaara, M., Ripatti, S., Pouta, A., Naluai, A. T., Olin, A. C., Toren, K., Cooper, M. N., James, A. L., Palmer, L. J., Hingorani, A. D., Wannamethee, S. G., Whincup, P. H., Smith, G. D., Ebrahim, S., McKeever, T. M., Pavord, I.D., MacLeod, A. K., Morris, A. D., Porteous, D. J., Cooper, C., Dennison, E., Shaheen, S., Karrasch, S., Schnabel, E., Schulz, H., Grallert, H., Bouatia-Naji, N., Delplanque, J., Froguel, P., Blakey, J. D., NSHD Respiratory Study Team, Britton, J. R., Morris, R. W., Holloway, J. W., Lawlor, D. A., Hui, J., Nyberg, F., Jarvelin, M. R., Jackson, C., Kahonen, M., Kaprio, J., Probst-Hensch, N. M., Koch, B., Hayward, C., Evans, D. M., Elliott, P., Strachan, D. P., Hall, I. P., & Tobin, M. D. (2010). Genome-wide association study identifies five loci associated with lung function. *Nature Genetics, 42*, 36–44.

Schroll, M. (2003). Physical activity in an ageing population. *Scandinavian Journal of Medicine & Science in Sports, 13*, 63–69.

StataCorp. (2009). *Stata statistical software: Release 11*. Texas: College Station.

Sharma, G., & Goodwin, J. (2006). Effect of aging on respiratory system physiology and immunology. *Clinical Interventions in Aging, 1*, 253–260.

Standardization of spirometry, 1994 update. American Thoracic Society. (1995). *American Journal of Respiratory & Critical Care Medicine, 152*, 1107–1136.

Steele, R. M., Finucane, F. M., Griffin, S. J., Wareham, N. J., & Ekelund, U. (2009). Obesity is associated with altered lung function independently of physical activity and fitness. *Obesity, 17*, 578–584.

Stern, D. A., Morgan, W. J., Wright, A. L., Guerra, S., & Martinez, F. D. (2007). Poor airway function in early infancy and lung function by age 22 years: A non-selective longitudinal cohort study. *Lancet, 370*, 758–764.

Sulander, T., Helakorpi, S., Nissinen, A., & Uutela, A. (2001). *Health behaviour and health among Finnish elderly, Spring 2001, with trends 1993–2001*. Finland: KTL — National Public Health Institute, Department of Epidemiology and Health Promotion, Health Promotion Research Unit. Retrieved from http://www.ktl.fi/publications/2001/b17.pdf

Tiainen, K., Sipila, S., Kauppinen, M., Kaprio, J., & Rantanen, T. (2009). Genetic and environmental effects on isometric muscle strength and leg extensor power followed up for three years among older female twins. *Journal of Applied Physiology, 10*6, 1604–1610.

Viljanen, A. (1982). Reference values for spirometric, pulmonary diffusing capacity and body plethysmographic studies. *Scandinavian Journal of Clinical Investigation,* (supplement 159), 5–50.

Vink, J. M., Willemsen, G., & Boomsma, D. I. (2005). Heritability of smoking initiation and nicotine dependence. *Behavior Genetics, 3*5, 397–406.

Wilk, J. B., Djousse, L., Arnett, D. K., Rich, S. S., Province, M. A., Hunt, S. C., Crapo, R. O., Higgins, M., & Myers, R. H. (2000). Evidence for major genes influencing pulmonary function in the NHLBI family heart study. *Genetic Epidemiology, 1*9, 81–94.

Zhai, G., Valdes, A. M., Cherkas, L., Clement, G., Strachan, D., & Spector, T. D. (2007). The interaction of genes and smoking on forced expiratory volume: A classic twin study. *Chest, 13*2, 1772–1777.

https://doi.org/10.1375/twin.14.5.401 Published online by Cambridge University Press