The Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults (SAPALDIA), a population cohort study, used heated-wire spirometers in 1991 and 2002 and then ultrasonic spirometers in 2010 revealing measurement bias in healthy never smokers. To provide a practical method to control for measurement bias given the replacement of spirometer in long-term population studies, we built spirometer-specific reference equations from healthy never smokers participating in 1991, 2002, and 2010 to derive individualized corrections terms. We compared yearly lung function decline without corrections terms with fixed terms that were obtained from a quasi-experimental study and individualized terms. Compared with baseline reference equations, spirometer-specific reference equations predicted lower lung function. The mean measurement bias increased with age and height. The decline in forced expiratory volume in 1 second during the reference period of 1991–2002 was 31.5 (standard deviation (SD), 28.7) mL/year while, after spirometer replacement, uncorrected, corrected by fixed term, and individualized term, the declines were 47.0 (SD, 30.1), 40.4 (SD, 30.1), and 30.4 (SD, 29.9) mL/year, respectively. In healthy never smokers, ultrasonic spirometers record lower lung function values than heated-wire spirometers. This measurement bias is sizeable enough to be relevant for researchers and clinicians. Future reference equations should account for not only anthropometric variables but also spirometer type. We provide a novel method to address spirometer replacement in cohort studies.

chronic obstructive pulmonary disease; lung function; population study

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults; SD, standard deviation; SSRE, spirometer-specific reference equation.

Long-term population studies on respiratory health face changes in available technology, often forcing investigators to use different spirometers over time. Current lung function equations are based on age, height, and sex, disregarding the effect of spirometers on lung volume measurements (1–4).

Spirometer comparison studies, as performed in specialized laboratory settings on human subjects or using flow volume generators, systematically showed small but significant differences between devices (5, 6). Although such discrepancies may have limited impact in clinical settings, epidemiologic research may be affected by even small systematic biases. Linear correction terms as derived from quasi-experimental studies might be applied. Nevertheless, fixed correction terms assume systematic biases to be independent of participants’ anthropometric characteristics or technician’s experience, which might not hold true. For example, certain spirometers prompt technicians to interrupt the test when technical criteria, such as “no flow,” are reached, while others rely on automatic procedures. These factors can impact on lung volume measurements and are not fully addressed by applying fixed
Spirometric data collection protocols for the 3 surveys are detailed in Web Appendix 1, available at http://aje.oxfordjournals.org/. To reduce unwarranted heterogeneity and possible biases and in accordance with previous derivations of reference values for lung function, we excluded from the SAPALDIA cohort current or former smokers and subjects with a history of wheezing in the last 12 months, shortness of breath at rest, nocturnal attack of shortness of breath, attack of asthma, current asthma medication, or a history of chronic cough or phlegm to define the healthy never smokers (1). From 9,143 subjects enrolled in 1991, 2,922 were healthy never smokers. Our definition of healthy never smokers is in line with the criteria proposed by Johannessen et al. (9), notably regarding history of smoking or respiratory symptoms.

Of the initial cohort, 1,951 healthy never smokers were re-assessed in 2002 and 1,513 in 2010–2011, providing a total of 6,386 spirometries. All spirometries in the present analyses were obtained from never smokers who were healthy at the time of the survey. Of 2,922 and 1,951 healthy never smokers in 1991 and 2002, 149 and 34 were, respectively, noneligible for the subsequent surveys because of interval smoking. A restricted subgroup of 861 healthy never smokers participated in all 3 assessments, providing 2,583 spirometries. The flowchart details subjects’ participation across surveys (Figure 1). The advantages of using all spirometries (n = 6,386), no matter how many times the healthy never smokers participated, relate to statistical power and precision in the reference equations as the sample size is substantially larger, particularly in older subjects, who are less likely to participate in follow-up surveys. Avoidance of selection bias related to nonparticipation at 1 survey because of transient respiratory symptoms and application of mixed linear model techniques taking into account missing values are other reasons why we opted for this larger data set. However, for comparison, we also derived SSREs based on the restricted subgroup with complete participation (n = 2,583). These results are shown in Web Appendix 1.

**Spirometry assessment**

Spirometry was measured with desktop heated-wire spirometers (SensorMedics, Yorba Linda, California) in 1991 (SAPALDIA 1) and 2002 (SAPALDIA 2) according to American Thoracic Society recommendations. Heated-wire spirometers were calibrated daily with a 3-L syringe at each participating center. Temperature was measured and used for correction to body temperature. The portable, ultrasonic EasyOne spirometers (ndd medizinotechnik AG, Zürich, Switzerland), which are widely used in epidemiologic research, were selected in 2010 (SAPALDIA 3). The ultrasonic device does not require formal calibration. Nevertheless, accuracy was verified and recorded daily by using a 3-L syringe. Accuracy records were systematically within the mandatory range of 3%. All spirometries considered in the present analyses were recorded without bronchodilation.

**Statistical methods**

We apply the following 3 approaches to derive percent predicted values for each survey.

**Method 1: cross-sectional reference equation.** The heated-wire spirometric data from 1991 were used to derive reference equations for forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced midexpiratory flow, and FEV1/FVC that were applied for the 3 surveys (1). The method, thus, does not correct for potential errors due to the replacement of spirometers at SAPALDIA 3.
Method 2: fixed additive correction terms. To estimate the measurement bias between spirometers’ type, we measured and compared lung volumes of 84 young healthy never smokers (mean age = 24 years), specifically enrolled for a spirometer comparison study. Gerbase et al. (6) estimated mean volume differences for FEV1, FVC, FEV1/FVC, and forced midexpiratory flow between ultrasonic and heated-wire spirometers using mixed linear models adjusted for age, sex, and height. Because interaction by sex was not observed in this comparison study, between spirometers’ differences were reported without sex stratification; thus, the fixed correction terms derived from this study were not sex specific. The obtained differences were used as fixed additive correction terms for lung volume in the SAPALDIA 3 survey. Percent predicted values were thereafter computed with the SAPALDIA 1 reference equations for all 3 surveys.

Method 3: spirometer-specific reference equations. To more fully integrate all sources of spirometer-related biases, this method is based on the derivation of novel reference equations, namely, 1 set of equations for the heated-wire spirometers and 1 for the new ultrasonic spirometers.

Spirometer-specific reference equations were based on serial lung function tests from healthy never smokers (SAPALDIA 1: n = 2,922; SAPALDIA 2: n = 1,951; SAPALDIA 3: n = 1,513). Mixed linear models with a random intercept for each subject were built with the following independent variables: age, age squared, height, sex, and spirometer type (heated wire or ultrasonic). The statistical models integrated interaction terms to obtain reference equations for both sex and spirometer types.

As a sensitivity analysis, we derived a second set of SSREs based on the restricted subgroup of healthy never smokers participating in all 3 surveys (n = 861) (Figure 1). Details are shown in Web Appendix 2.

Derivation of individualized spirometer-specific correction terms. Using our SSREs, we derived correction terms for each subject, taking into account the type of spirometer, as well as the interaction between spirometer types and anthropometric variables such as height, sex, and age. Indeed, for each subject, we were able to compute 1 reference value for the heated-wire spirometer and 1 for the ultrasonic spirometer, for all spirometric parameters. Differences between these 2 values were used as an individualized correction term for the spirometric parameters of each subject. One example is provided in Web Appendix 3 and Web Table 1.

RESULTS

Subject characteristics

Web Table 2 displays the characteristics of the entire cohort and the subset of healthy never smokers at the 3 surveys. From 2,922 healthy never smoker subjects participating at SAPALDIA 1, 1,951 at SAPALDIA 2, and 1,513 at SAPALDIA 3, 42%, 41%, and 44%, respectively, were males. Healthy never smokers eligible for the present analysis were younger (SAPALDIA 1 age difference: 2.56 (95% confidence interval (CI): 2.03, 3.09) years; SAPALDIA 2: 1.70 (95% CI: 1.07, 2.33) years; SAPALDIA 3: 2.17 (95% CI: 1.48, 2.86) years) and more likely to be women (SAPALDIA 1: odds ratio = 1.52 (95% CI: 1.39, 1.67); SAPALDIA 2: odds ratio = 1.56 (95% CI: 1.40, 1.74); SAPALDIA 3: odds ratio = 1.44 (95% CI: 1.27, 1.63)) compared with subjects who were noneligible.

Differences in predicted lung function

Table 1 shows the mean predicted values and observed values in percent predicted for lung function at the 3 surveys as computed by using the SAPALDIA 1 cross-sectional reference equations (1) and the SSREs for healthy never smokers. The SAPALDIA 1-based reference equations predicted larger

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**Figure 1.** Study subjects’ flowchart showing participation by heated-wire (HW) and ultrasonic (US) spirometer, SAPALDIA Cohort, 1991–2010. Data from healthy never smokers (HNS) with at least 1 spirometry measure were used for the main analysis and are shown in the third column. From those, a restricted subgroup (n = 861) were consistently healthy and had spirometry measures in all 3 surveys: SAPALDIA 1 (1991), SAPALDIA 2 (2002), and SAPALDIA 3 (2010). SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults.
Table 1. Mean Predicted Values and Mean Observed Percent Predicted Values for FEV₁, FVC, FEV₁/FVC, and FEF₂₅₋₇₅ for Male and Female Healthy Never Smokers, SAPALDIA Cohort, 1991–2010

<table>
<thead>
<tr>
<th>Lung Function Parameter</th>
<th>SAPALDIA 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SAPALDIA 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>SAPALDIA 3&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS</td>
<td>SSRE</td>
<td>CS</td>
</tr>
<tr>
<td>FEV₁</td>
<td>4.290 (0.50) 100.3 (11.8)</td>
<td>4.276 (0.48) 100.6 (11.9)</td>
<td>3.980 (0.49) 98.2 (12.3)</td>
</tr>
<tr>
<td>FVC</td>
<td>5.349 (0.52) 100.3 (11.7)</td>
<td>5.351 (0.48) 100.2 (11.6)</td>
<td>5.149 (0.56) 99.6 (12.1)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>80.18 (3.07) 100.1 (8.0)</td>
<td>79.98 (3.48) 100.4 (8.0)</td>
<td>77.22 (2.8) 98.6 (7.8)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅</td>
<td>4.065 (0.67) 104.1 (27.6)</td>
<td>4.157 (0.75) 102.1 (27.3)</td>
<td>3.475 (0.67) 97.2 (28.4)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>3.033 (0.38) 101.2 (13.4)</td>
<td>3.064 (0.38) 100.2 (13.3)</td>
<td>2.741 (0.44) 100.4 (13.5)</td>
</tr>
<tr>
<td>FVC</td>
<td>3.765 (0.38) 100.5 (13.5)</td>
<td>3.785 (0.37) 99.9 (13.4)</td>
<td>3.536 (0.47) 101.1 (13.2)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>80.78 (3.6) 100.5 (7.6)</td>
<td>80.88 (4.2) 100.4 (7.7)</td>
<td>77.51 (3.3) 99.1 (7.6)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅</td>
<td>3.025 (0.59) 104.4 (28.1)</td>
<td>3.115 (0.64) 101.7 (27.6)</td>
<td>2.490 (0.64) 99.3 (30.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CS, cross-sectional reference equations based on heated-wire spirometer; FEF₂₅₋₇₅, forced midexpiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults; SD, standard deviation; SSRE, spirometer-specific reference equation.

<sup>a</sup> SAPALDIA 1 included 1,213 men and 1,709 women in 1991.
<sup>b</sup> SAPALDIA 2 included 791 men and 1,160 women in 2002.
<sup>c</sup> SAPALDIA 3 included 665 men and 848 women in 2010.
FEV\textsubscript{1} and FVC values at SAPALDIA 3 compared with the SSRE. For men, the mean differences in prediction were 0.266 L (difference, 6.7\%) for FEV\textsubscript{1} and 0.443 L (difference, 9.3\%) for FVC. The larger measurement bias between spirometer types for FVC compared with FEV\textsubscript{1} led to a higher average FEV\textsubscript{1}/FVC ratio in percent predicted at SAPALDIA 3 (i.e., 102.2\% in men, 102.6\% in women) when the SAPALDIA 1-based reference equations were applied. Web Table 3 displays mean predicted values and observed values in percent predicted for lung function in the restricted subgroup participating in all 3 surveys. The differences in prediction were of similar size compared with those of the main analysis.

Figure 2 shows the observed values (dots) for lung function across age ranges for healthy never smokers. The graphs also display the predicted mean value over age for a subject of mean height (163 cm for women and 175 cm for men) with the SAPALDIA 1-based reference equations (Figure 2A), the SSREs for ultrasonic spirometers (Figure 2B), and heated-wire spirometers (Figure 2C). Overall, ultrasonic spirometers measured lower lung volumes among healthy never smokers.
This bias increased with age. For example, for a man of 175 cm, FVC differences between predicted values were 0.138 L at age 30 years and 0.464 L at age 60 years.

Web Figure 1 shows the predicted mean lung function over age, as predicted by the SAPALDIA 1-based reference equations, the SSREs using either subjects participating in at least 1 survey, or the restricted subgroup participating in all 3 surveys. Only slight differences were observed at the extremes of age range when the equations derived from the base population of healthy never smokers and the restricted subgroup were compared.

**Effect of fixed correction terms**

Correction terms or heated-wire (HW) and ultrasonic (US) spirometers, as computed from our quasi-experimental study,
were as follows (6):

\[
\begin{align*}
\text{FEV}_1(\text{HW}) &= \text{FEV}_1(\text{US}) + 0.055 \text{ L} \\
\text{FVC}(\text{HW}) &= \text{FVC}(\text{US}) + 0.0832 \text{ L} \\
\text{FEF}_{25-75}(\text{HW}) &= \text{FEF}_{25-75}(\text{US}) - 0.026 \text{ L/second} \\
\text{FEV}_1/\text{FVC}(\text{HW}) &= \text{FEV}_1/\text{FVC}(\text{US}) - 0.0039 ,
\end{align*}
\]

where \( \text{FEF}_{25-75} \) is the forced midexpiratory flow.

Adding these fixed corrections terms to the SAPALDIA 3 values did not fully correct for the observed measurement differences.

**Spirometer-specific equation predictions**

The SSREs are shown in Web Appendix 1, separately for heated-wire and ultrasonic spirometers.

**Application of individualized correction terms to adjust for lung function decline**

Table 2 shows the mean annual lung function decline among the 3 surveys of SAPALDIA in healthy never smokers and in the entire cohort.

Although the mean annual FEV\textsubscript{1} loss was 31.5 (standard deviation (SD), 28.7) mL/year between 1991 and 2002 (reference period with identical spirometers), FEV\textsubscript{1} loss increased to 47.0 (SD, 30.1) mL/year between 2002 and 2010 for healthy never smokers after spirometer change. A larger mean annual loss between 2002 and 2010 was also observed for FVC (2002–2010: 65.6 (SD, 46.4) mL/year vs. 1991–2002: 19.1 (SD, 37.8) mL/year).

Correction of ultrasonic measurements with the fixed correction term did not much remove the discrepancies observed in the uncorrected decline among these healthy never smokers.

In contrast, SSRE individualized correction terms yielded values of lung function decline for the 2002–2010 period comparable to those of the reference period. After application of the spirometry-specific correction terms at SAPALDIA 3, we observed in healthy never smokers a mean annualized loss of 30.4 (SD, 29.9) mL/year for FEV\textsubscript{1} and 27.2 (SD, 44.0) mL/year for FVC in healthy never smokers.

**DISCUSSION**

The replacement of heated-wire by ultrasonic spirometers in the third assessment of SAPALDIA, a population-based adult cohort, caused a systematic drop of lung volume measurements in healthy never smokers. On average, measurements of FVC by the ultrasonic spirometer in older healthy never smokers were up to 450 mL inferior to the values predicted by reference equations based on previous data from the same cohort but
obtained with heated-wire spirometers. As a consequence, lung function decline appeared considerably larger between the second and third surveys after spirometer replacement compared with the reference period. These large differences between heated-wire and ultrasonic spirometers were unexpected. Bench comparison studies of spirometers, using a mechanical flow volume generator, consistently showed good agreement between devices. Our extensive comparisons of devices, done in young healthy never smokers, already indicate that certified devices may provide systematically different values (6, 7). However, no large-scale spirometer comparison studies including older subjects have been performed so far. These differences were not explained by the “healthy participation bias” one could hypothesize to be introduced in using all data of all participants, as the same pattern emerges in the analysis based on the restricted subgroup with complete participation in all 3 surveys (refer to the Web appendixes).

**Anthropometric variables associated with measurement bias**

Bias due to spirometer replacement was larger for subjects who were old, male, and tall and for those with larger lung volumes. Our study is the first to suggest that biases in spirometer measurements are related not only to the device but also by a function of complex interactions between devices, age, sex, and height. Age is the strongest predictor of unexpected lower lung volume when measured with ultrasonic spirometers compared with heated-wire spirometers.

No straightforward technical cause was identified to explain the observed differences. We observed that handheld ultrasonic spirometers let patients bend forward during and at the end of the expiratory maneuver, which was not possible with the desktop heated-wire spirometers. So, older subjects might be more prone to bend during the maneuver and may therefore be less able to exhale with full force. Although technicians were clearly instructed not to allow bending, preventing the change in body position was not always possible with handheld spirometers, whereas the heated-wire spirometers forced subjects to remain in a stabilized and fixed position.

**Fixed additive correction terms**

Fixed additive correction terms were insufficient to correct for measurement bias in our study. Because bias grows with age and other factors such as height or lung volume, spirometer validation studies enrolling only young subjects failed to characterize the differences due to age and the other factors. Interestingly, our novel approach revealed that bias was minimal in younger healthy never smokers (quite often the age of participants volunteering to device comparison tests) and largest for the oldest ones, which is in line with the comparison study we performed earlier (6).

**Spirometer-specific reference equations and individualized correction terms**

We developed SSREs and derived individualized spirometer-specific correction terms, which were able to control for the spirometer replacement in our longitudinal study. Using our SSREs, we found that lung volumes were close to 100% of the predicted value in healthy never smokers, independently of age, survey, or spirometer type. Most relevantly for longitudinal studies, our novel method resulted in very plausible and consistent lung function decline over all 3 surveys of SAPALDIA. Our approach also comes with the advantage of fully capitalizing on the much larger sample size available in the main study, which experimental comparison studies never can achieve.

**Implications for epidemiologic research**

When faced with the inevitable replacement of spirometers because of obsolescence in long-term epidemiologic studies, researchers should plan the approaches and methods to correct for such systematic errors. Although direct comparison studies provide insight into the possible degree of differences, the derivation of simple correction terms from such small studies is unlikely to be sufficient. As shown, the deviations between devices are explained by a range of factors. Our novel method (i.e., SSRE) is instead very powerful and versatile as it allows taking into account a whole range of study-specific factors. Our approach can be applied to other cohort studies as it is based solely on the data collected in such cohorts by default. In fact, as shown, formal device comparison tests do not comprehensively correct the biases, as those originate not only from the device per se but also from the interactions among devices, participants, and possibly the field-worker. A question to be clarified in the application of our approach in other cohort studies is the definition of the subgroup to define SSRE, as this may have an impact on the absolute values and, thus, the final lung function data and their distribution. We recommend restriction on healthy never smokers, but we realize that other studies may have other criteria by which to define “healthy” (9). As long as identical definitions can be applied to all surveys, such differences may not be relevant.

**Implications for clinical practice**

Our study also has implications for every day clinical practice. Diagnosis of lung disease and response to treatment rely on reference equations derived with spirometer technologies that have evolved over the years and are sometimes not in use anymore. Our study calls for caution in evaluation of the lung function of patients in case of replacement of the spirometer. As shown, such comparisons might be particularly misleading in older patients. The impact of using different spirometer technologies on the interpretation of lung function has been evoked in other studies (10).

**Sensitivity analysis**

There is also a need to define the “reference populations” for establishing SSREs with regard to loss to follow-up and nonresponse. Ideally, one would opt for using a well-defined subpopulation of healthy never smokers that provided spirometry data in all surveys for which reference equations need to be derived. Although such “perfect participants” may not necessarily be representative of healthy never smokers in general, it is the experimentally cleanest group to base a device
comparison upon at the cost of decreased statistical power and precision. We analyzed a large number of high-quality spirometries performed over 20 years on the same cohort of healthy never smokers participating in 1 or more surveys, thus reducing within-subject variability. We reestimated our SSREs, based on the restricted subgroup of subjects participating at all 3 surveys of SAPALDIA. As shown in our analyses, the use of all healthy never smokers versus only those with complete (3 times) participation was of marginal relevance for our SSREs; thus, we conclude that, in the case of concerns about precision and statistical power, one may relax the definition of the reference population and include healthy never smokers with data from at least 1 spirometry test.

**Strengths and limitations**

Although our results fit the needs of longitudinal analyses of the SAPALDIA data, our SSREs and the derived correction terms may not be generalizable to other data sets. However, our approach is applicable to other studies, using the study-specific data and devices. Because SAPALDIA 1 cross-sectional reference equations were established with healthy never smokers aged 18–60 years, extrapolation to older subjects is questionable. Indeed, cross-sectional reference equations predicted larger-than-observed lung volumes in the third survey among healthy never smokers who were older. Our SSRE covers a large age range from 18 to 81 years and, thus, has the advantage of providing reference values without extrapolation for older age groups.

The effect of bronchodilation was not tested in our study. Bronchodilation increases lung volumes in subjects with pre-existing lung disease, mostly asthma. It has been shown in other population studies that chronic obstructive pulmonary disease prevalence was reduced by 27% if bronchodilation was applied as required to correctly define the disease (11). Nevertheless, studies on response to bronchodilators in healthy never smokers are sparse. A Canadian study including healthy never smokers with normal lung function found an upper limit of 9% change after bronchodilation (12). A study from Norway found a larger bronchodilator response in younger age and taller subjects (13). Because bronchodilation may increase lung volumes in healthy never smokers and because between-spirometer differences increase with lung volume, it can be expected that even larger between-spirometer differences would have been observed in our cohort if bronchodilation had been performed.

**Conclusions**

In an elderly general population, we found that measurements by ultrasonic spirometers provide lower lung volume than those by heated-wire spirometers. Measurement bias related to spirometer is large enough to be relevant for researchers and clinicians confronted with technological changes. Spirometer (or software) replacement should be avoided in epidemiologic longitudinal studies and, if inevitable, should be addressed early in study planning. We provide a promising method to correct longitudinal biases via the derivation of spirometer-specific reference equations.

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