



GLI-2012 reference equations for spirometry in the Norwegian population

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Key Words:	spirometry reference values, Adolescence, Adult

GLI-2012 reference equations for spirometry in the Norwegian population

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Key words: spirometry, reference values, adolescents, adults

Take-home message: GLI-2012 all-age reference values for spirometric indices fit Norwegians aged
12-85 years

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Abstract

Background: We studied the fit of the Global Lung Function Initiative all-age reference values to Norwegians, compared them with currently used references (European Community for Steel and Coal (ECSC) and Zapletal) and estimated the prevalence of obstructive lung disease.

Methods: Spirometry data collected in 30,239 subjects (51.7% females) aged 12-90 years in three population-based studies were converted to z-scores.

Results: Healthy non-smokers comprised 2,438 adults (57.4% females) aged 20 – 90 and 8,725 (47.7% female) adolescents aged 12-19 years. The GLI-2012 prediction equations fitted the Norwegian data satisfactorily. Median (SD) z-scores were respectively 0.02 (1.03), 0.01 (1.04) and -0.04 (0.91) for FEV₁, FVC and FEV₁/FVC in males, and -0.01 (1.02), 0.07 (0.97) and -0.21 (0.82) in females. The ECSC and Zapletal references significantly underestimated FEV₁ and FVC. Stricter criteria of obstruction (FEV₁/FVC < the GLI-2012 lower limit of normal (LLN)) carried a substantially higher risk of obstructive characteristics than FEV₁/FVC < 0.7 and > GLI-2012 LLN. Corresponding comparison regarding myocardial infarction showed a fourfold higher risk for women.

Conclusion: The GLI-2012 reference values fit the Norwegian data satisfactorily and are recommended for use in Norway. Correspondingly, the FEV₁/FVC GLI-2012 LLN identifies higher risk of obstructive characteristics than FEV₁/FVC < 0.7.

Introduction

Spirometry is pivotal for the diagnosis and follow-up of patients with obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Results are often reported as percent predicted where predicted values are obtained from a healthy reference population. However, predicted values from different sources may differ widely, and as the variability of measurements varies with age the use of percent of predicted leads to an age bias(1). The latter can be circumvented by the use of sex, age, height and ethnicity specific z-scores, which define how many standard deviations a measurement differs from the predicted value (2). It is important to use prediction

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3 equations that fit the population. In Norway, equations have been developed for adults by Gulsvik *et*
4 *al.* [study population 18-23 years (n=480) (3), Johannessen *et al.* [study population 26-82 years
5 (n=515)] (4) and Langhammer *et al.* [study population 20-80 years (n=908)] (5). Nevertheless, the
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7 equations from the European Coal and Steel Community (ECSC) [study population 18-70 years] (6)
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9 are widely used despite having been found to underestimate normal lung function in Caucasians (4, 5,
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11 7-9). For children and adolescents the equations developed by Zapletal *et al.* [study population 6-17
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13 range (n=111)] (10) and Polgar *et al.* [study population 6-18 years] (11) are commonly used. The
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15 ECSC and Polgar equations were constructed from published reference equations rather than from
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17 actual measurements. Use of different reference values within and between pulmonary function
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19 laboratories introduces inconsistencies in reported predicted values for individual patients, as do the
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21 disjunctions between reference values developed for different age groups (12).
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25 In 2012, the Global Lung Function Initiative (GLI) published reference values for the age range 3 to
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27 95 years for several ethnic groups. For Caucasians the values were based on 57,395 individuals (2).
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29 The fit of these reference values has been tested in some populations, and reported results have been
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31 conflicting (13-17). Ben Saad *et al.* reported that GLI-2012 overestimated FEV₁ and FVC in a North-
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33 African adult population (14), possibly because of contribution of sub-Saharan ancestry of Berbers,
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35 while recent studies found that GLI-2012 underestimates both FEV₁ and FVC in adults in Finland and
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37 Sweden (13, 17). Few studies have evaluated the fit of GLI-2012 over a large age span; a large study
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39 including Australasian Caucasians aged 4-80 years reported the differences to be less than the within
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41 test variation accepted in spirometry testing (16).
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44 Use of different predicted values also results in different estimates of prevalence of lung disease.
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46 Peradzynska *et al.* found that in children referred to hospital for respiratory symptoms or disease,
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48 GLI-2012 resulted in a higher proportion with lung function abnormalities compared to use of Polish-
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50 1998 reference values (18). Transition from Hankinson (9) and Wang (19) equations to GLI-2012 lead
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52 to grossly similar prevalence rates of abnormally low values for FEV₁, FVC, and FEV₁/FVC in
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54 hospital based settings, but disparate results (20, 21) when compared to equations from Polgar (11),
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56 and Zapletal (10).
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3 We aimed to study the fit of GLI-2012 in a reference sample of healthy never-smoking Norwegians,
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5 by firstly developing prediction values based on a reference sample (Nor-2015), and then evaluating
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7 how these reference values agree with GLI-2012 in comparison with other currently used prediction
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9 equations in Norway. Additionally, we aimed to estimate the prevalence of respiratory and
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11 cardiovascular symptoms and disease in the general population using different criteria for bronchial
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13 obstruction.

14 15 16 17 18 **Methods**

19 20 **Study population and measurements.**

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23 We generated a reference sample of participants randomly selected from three Norwegian population
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25 based studies; the Tromsø 6 Study (22), the Hordaland County Cohort Study (HCCS) (23), and the
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27 Nord-Trøndelag Health Study (HUNT) with HUNT2 and HUNT3 for adults, and YoungHUNT1,
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29 YongHUNT2 and YoungHUNT3 for adolescents (24, 25) (table 1). In total, 15,615 persons aged 12-
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31 19 years and 14,624 persons aged 20-90 years performed pre-bronchodilator (pre-BD) spirometry. In
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33 all studies, the participants answered comprehensive questionnaires regarding life style, symptoms and
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35 diseases. Height and weight were measured with light clothing and without shoes, height to the nearest
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37 cm in HCCS, to the nearest half centimeter in HUNT2/YoungHUNT1 (1995-1997) and
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39 YoungHUNT2 (2000-01), and with one decimal in Tromsø and HUNT3/YoungHUNT3 (2006-2008).
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41 Age at spirometry was registered without decimals in Tromsø, in HUNT and HCCS with one decimal.

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44 Persons having participated more than once had spirometry and corresponding data included only
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46 from their latest participation. HUNT3 invited the entire adult population of the county, and among the
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48 50,807 participants, the Lung Study invited a 10 % random sample of all participants, and persons
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50 reporting symptoms, diagnosis or use of medication for asthma or COPD to spirometry.

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53 Three different types of spirometers were used for pre-bronchodilator (Pre-BD) FEV₁ and FVC (table
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55 1). In the HCCS and the Tromsø studies the measurements were performed at centralized examination
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3 stations (26), while in HUNT, spirometry was performed by adolescents at schools, and in adults at
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5 examination stations in all 24 municipalities of the county.
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8 All centers performed spirometry according to the 1994 ATS-criteria (27). All spirometers were
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10 calibrated each morning and afternoon with a one or three litre syringe; the participants were seated,
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12 wore nose clips, and received standardized instruction from the technician. At least three spirometric
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14 maneuvers were performed and the test considered satisfactory when the two largest FEV₁ and FVC
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16 differed by less than 200 mL; the Tromsø Study, however, aimed at differences below 150 mL. The
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18 highest FEV₁ and FVC were selected and used to calculate the FEV₁/FVC ratio. Room temperature
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20 ranged from 19 to 24 °C.
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26 **Quality control**

27 In HUNT, the spirometry software provided feedback on acceptability of technique and repeatability.

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29 For spirometry from HUNT3/YoungHUNT3, curves were scored grade A-F partly in line with a
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31 recent study by Hankinson *et al.* (28). All curves graded A-C were included in the study; meaning at
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33 least two acceptable blows with less than 200 mL difference, but we did not apply the end of test
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35 criterion with exhalation > 6 s. Among adolescents short expiration time made evaluation of end of
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37 test difficult, thus only smoothly ending flow-volume curves with FEV₁/FVC ≤ 0.95 were accepted.

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39 Thorough quality assessments were also performed in HCCS and the Tromsø Study; in the latter
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41 inter- and intra-observer agreements showed excellent results (29).
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47 **Statistics**

48 The healthy reference sample comprised persons without self-reported respiratory disease, cardinal
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50 respiratory symptoms, smoking history and other respiratory symptoms (23). Z-scores of lung indices
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52 according to predicted values by GLI-2012 were calculated for all participants and means and standard
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54 deviations (SD) reported.
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3 If the GLI-2012 equations are appropriate for healthy Norwegians mean (SD) z-scores should
4 approximate 0 (1) across the entire age and height range studied. Data were stratified by sex and
5 reported by study site, age and height.
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9 Predicted values derived from the total Norwegian dataset of healthy subjects (Nor-2015) were
10 estimated in the same manner as GLI-2012 using the statistical software R (version 2.15.1) with the
11 generalized additive model for location, scale and shape package (GAMLSS). We applied the LMS
12 method, a statistical method to normalize skewed distributions using a smoothing trend curve; the
13 resulting Box-Cox-Cole Green power lambda (L), and the similarly smoothed median mu (M) and
14 coefficient of variation sigma (S) summarize the distribution of the data (30).
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22 Predicted values and z-scores (observed minus predicted/standard deviation) were also calculated
23 according to the equations from Johannessen, Gulsvik, Langhammer, ECSC and Zapletal, restricted to
24 the relevant age range. The agreement with GLI-2012 and other reference values was visualized by
25 Bland-Altman plots.
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30 We looked at two definitions for airflow obstruction, $FEV_1/FVC < 0.70$ (which is commonly used in
31 Norwegian clinical practice) and $FEV_1/FVC < LLN$ as recommended by ATS/ERS (31) in order to
32 compare their COPD prevalences and associations with symptoms.
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37 The proportion of males and females in the general population with an obstructive pattern was
38 estimated by use of GLI-2012 and Nor-2015 in all participants in HUNT3 based on inverse weighting
39 of the probability of having been selected for spirometry (supplement figure 1). Further the age
40 adjusted risk of reporting symptoms or diseases by the stricter criteria of obstruction, $FEV_1/FVC <$
41 LLN , compared to $FEV_1/FVC < 0.7$ and $\geq LLN$ was estimated by binary logistic regression models.
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50 Results

51 In total, 1403 females and 1035 males aged 20 - 90 years met the selection criteria for the reference
52 sample; corresponding figures for age group 12-19 years were 4404 girls and 4654 boys (table 2). The
53 mean age of included adult women and men was lower in HUNT (49 and 45 years) compared to
54 Hordaland (56 and 52 years) and Tromsø (63 and 61 years). The percentages of the total sample
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3 included in the healthy reference population were 15.1 in Tromsø, 15.9 in Hordaland, 18.7 in HUNT
4 and 62.4 in YoungHUNT (supplement table 1).
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8 In the reference sample of healthy individuals the distributions of z-scores for the different indices
9 stratified by sex and age below and above 20 years were close to normal. There was no relevant
10 correlation in the reference population between the z-scores for FEV₁, FVC and FEV₁/FVC according
11 to GLI-2012 and age and height (explained variance 0.08% - 1.8%), but the FEV₁ and FVC tended to
12 be somewhat below predicted in the smallest boys (figure 1). The median(SD) z-scores for FEV₁, FVC
13 and FEV₁/FVC in females were -0.01 (1.02), 0.07 (0.97) and -0.12 (0.82), and in males 0.02 (1.03),
14 0.01 (1.04) and -0.04 (0.91), respectively. Stratification by age 20 years revealed closer fit among
15 adolescents than adults with z-scores for all indices close to zero except for median z-FEV₁/FVC (-
16 0.11) in girls. In adults, the fit to GLI-2012 was closer in men than in women, but for both sexes, a
17 slightly higher positive z-FVC than z-FEV₁ resulted in a negative median z-FEV₁/FVC.
18 Corresponding medians and fifth and 95th percentiles are reported in table 3.
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31 Plots of GLI-2012 z-scores by study site, age and height categories showed minor differences
32 between study sites, but confirmed a slightly lower z-FEV₁/FVC in women except in HUNT (figure
33 1). In women, z-FEV₁ and z-FVC were slightly higher at age 40-79, while FEV₁/FVC z-scores were
34 slightly lower in all age groups. In men, there was a good fit of GLI-2012 for all indices, independent
35 of age. In women with height 155–185 cm and men taller than 165 cm there was good fit of GLI-2012.
36 The Bland-Altman plots showed that predicted values from Zapletal for adolescents and ECSC for
37 adults underestimated the lung indices, while there was fairly close agreement between Nor-2015 (12-
38 90 years) and GLI-2012 (figure 2). Similar plots comparing Norwegians reference values (Gulsvik,
39 Langhammer and Johannessen) with GLI-2012 show rather good agreement for women for FEV₁ and
40 FVC. In men, however, the plots reveal somewhat higher levels of predicted FEV₁ from the
41 Norwegian sets, but rather inconsistent patterns and relatively large differences for predicted FVC
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Proportion with lung indices below lower limit of normal in the healthy and the general population

Ideally, about 5% of observations should fall below the GLI-2012 fifth percentile in the healthy population. GLI-2012 fit adolescents rather well, less so in adults, especially for FVC (table 3). For FEV₁ 2.4% of males and 3.1% of females of observations were below LLN, corresponding figures for FEV₁/FVC were 3.3 and 3.7%.

Based on estimates of the weighted sample (supplement figure 1); in the age range associated with the highest prevalence of COPD (40-80 years), 13.5 % of men and 9.3% of women had pre-BD FEV₁/FVC < 0.70, and 6.6% of both sexes for FEV₁/FVC < LLN defined by GLI-2012. Among those with pre-BD FEV₁/FVC < LLN according to Nor-2015 (n=3353) and GLI-2012 (n=3526), median z-scores (SD) for FEV₁ were -1.68 (1.19) and -1.62 (1.11), and for FEV₁/FVC -1.99 (0.70) and -2.08 (0.62), respectively.

More women and men were defined as obstructive according to FEV₁/FVC <0.70 compared to FEV₁/FVC <LLN according to Nor-2015 and GLI-2012 (table 4). In subjects identified with an obstructive pattern by GLI-2012 and Nor-2015 there was close agreement with self-reported obstructive lung disease in men, whereas in women disease and symptom prevalence were somewhat lower for GLI-2012 than for Nor-2015 (table 4). About one third reported a doctor diagnosis of asthma and one-fifth a doctor diagnosis of COPD, emphysema or chronic bronchitis.

For both sexes the age adjusted odds ratio for having obstructive lung disease related attributes was significantly higher in those with FEV₁/FVC<LLN compared to those with FEV₁/FVC<0.7 but \geq LLN (Table 5). The mean age for the first category was 49.8 years in women and 52.8 years in men, and corresponding figures for the last category were 70.8 and 67.3 years. The same comparison for cardiovascular diseases found the odds ratio for myocardial infarction increased in those with FEV₁/FVC<LLN but only for women.

Discussion

The main finding in this study is that the GLI-2012 equations fit a Norwegian population; differences between predicted and observed values are small, they are unrelated to age and height, and the scatter is close to that in GLI-2012 equations except for the FEV₁/FVC ratio in females, where it is smaller.

The reference group of adolescents outnumbers that of adults nearly fourfold (table 2), so that the closer fit in adolescents might relate to sample size. This study also confirms previous reports that the ECSC and Zapletal predicted values do not fit a healthy white population and lead to misclassification of subjects.

In men, the weighted prevalence of respiratory symptoms, diagnoses and use of medication among all HUNT3 participants were similar among those defined with an obstructive pattern according to GLI-2012 and Nor-2015. In females, the corresponding prevalence was lower for GLI-2012 than for Nor-2015 defined obstruction; this is to be expected as reference values derived from the population will fit that population better than external reference values.

The strength of the current study is the population-based design, recruiting randomly selected persons who performed spirometry according to international recommendations. Additionally, data were available on respiratory disease, symptoms and smoking history needed for selection of a healthy never-smoking reference group. The number of adolescents and elderly adults was large compared to other studies. In line with GLI-2012's recommendation, in this study height and age were measured with one decimal accuracy to avoid potential bias related to inaccuracies in these measures (32). Another strength of this study is the availability of reported symptoms, diagnosis and use of asthma medication for the entire HUNT3 population (n=50,807), from which subsamples reporting symptoms or a diagnosis of obstructive lung disease were additionally invited to spirometry. This provided an opportunity to estimate symptom prevalence by persons identified as obstructed by criteria. The prevalence of self-reported symptoms and diseases in the weighted sample agreed well with the source data for all participants (supplement table 2). We have found that using FEV₁/FVC<LLN to define airflow obstruction better identified subjects with relevant respiratory symptoms and disease attributes than did using the fixed ratio of <0.7 to define airflow obstruction. Our finding of a fourfold

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3 increased risk of myocardial infarction in women meeting the LLN definition compared to those
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5 above LLN and below the fixed ratio requires further investigation as opposite results have been
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7 reported by other studies (33). Among limitations, it is a challenge getting good quality spirometry
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9 curves in a large study carried out in different centers over many years. Many adolescents had a rather
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11 abrupt end of the exhalation, and in order to avoid underestimation of FVC and overestimation of
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13 FEV₁/FVC we excluded persons with a ratio above 0.95; however, this selection bias might explain
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15 the negative association of FEV₁ and FVC with height in younger subjects (figure 1). In addition, a
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17 low participation rate of 54% for adults in HUNT3 could point to selection bias. A non-participation
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19 study reported some healthy selection bias; chronic diseases such as diabetes, cardiovascular disease
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21 and COPD were more prevalent in the general population compared to participants (34). This should,
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23 however, not lead to bias in the healthy reference population, but will contribute to some
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25 underestimation of obstructive pattern in the entire population of the county. A disjunction in
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27 measured values from adolescence to adulthood probably arose from a selection bias; in the 20-29-
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29 years age range, participation rate was only 26% and 38% in males and females. Comparisons of the
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31 prevalence estimates for COPD between the present and other studies should take into consideration
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33 our use of pre-BD spirometry and not post-BD spirometry as recommended by GOLD (35) .
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37 During the last decades many prediction equations for spirometry have been published with large
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39 differences between them. This has partly been explained by technical, procedural and biological
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41 differences, and by sampling errors as well as differences in selection of reference groups (36). Some
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43 disagreements are related to different statistical software and modelling facilities; new statistical
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45 methods such as GAMLSS, however, have improved modelling by taking into account the non-linear
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47 relationship between age, height and spirometric indices, including a smooth transition from
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49 adolescence to adulthood, as well as modelling the age dependence of measurement variability. The
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51 present study found only minor differences between study sites and correspondingly between different
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53 spirometers. Such differences might arise from sampling error. The different patterns revealed when
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55 comparing previous Norwegian reference values with GLI-2012, especially among men, emphasize
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57 the importance of representative and large reference samples.
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3 The reference sample included in the present study is large enough to develop prediction values for
4 Norwegians aged 12 to 90 years, in line with previous recommendations of updated and regionally
5 developed reference values. In subjects with respiratory symptoms, there was fair agreement in z-
6 scores whether derived from GLI-2012 or Nor-2015 equations. A new equation specifically for
7 Norwegians will exploit the idiosyncrasies of the data and lead to a small improvement in the fit to this
8 particular population sample at the expense of a smaller valid age range and applicability to other
9 ethnic groups. Norway includes a Sami population of about 40,000 persons, and there is increasing
10 immigration from other ethnic groups, challenging the choice of reference values in daily clinical
11 practice. Whereas reference intervals and lower limits of normal provide some guidance, there is no
12 sharp demarcation of measurements in healthy and pathological conditions, so that decision limits also
13 hinge on clinical considerations (37). In order to simplify comparative studies between countries,
14 avoid confusion due to age-related gaps in reference values, and ease the conversion to reference
15 values for different ethnic groups, we recommend implementation of GLI-2012 in health care at all
16 levels in Norway. Although no data from children younger than 12 years were available, there is no
17 reason to believe that GLI-2012 would not fit that age range.
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36 **Conclusion**

37 GLI-2012 fits the Norwegian reference sample satisfactorily and shows superiority compared to the
38 ECSC and Zapletal reference values that are widely used in Norway. Advantages are a large age span
39 and inclusion of reference values for different ethnic groups. Therefore, we recommend
40 implementation of GLI-2012 in Norwegian health care.
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4 University of Norway in collaboration with the Norwegian Institute of Public Health, the University
5 Hospital of Northern Norway (UNN) and Tromsø City Council.
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14 Health.
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Table 1

Characteristics of persons randomly selected for spirometry by study site and equipment used in the Hordaland County Cohort Study (HCCS), the Tromsø Study and the Nord-Trøndelag Health Study (HUNT).

Study and Year	N (%female)	Age Range (Years)	Height range (cms)	Equipment
HCCS 1996-97 and 2003-05	2478 (51.6)	26-90	145-202	Vitalograph S-model ¹
The Tromsø 6 Study 2007-08	6437 (57.0)	38-87	140-193	Sensor Medics Vmax Encore ²
HUNT2 1995-97 and HUNT3 2006-08	5709 (54.4)	20-95	143-197	Heated pneumotachograph
YoungHUNT1 1995-97, YoungHUNT2 2000-01 and YoungHUNT3 2006-08	15615 (49.4)	12-19	135-204	MasterScope versions 4.15 & 4.25

¹ Although the Vitalograph chart stopped moving after 6 seconds, the subjects were asked to continue to exhale beyond 6 seconds to reach their FVC. The highest volume was then registered.

²Flow measured by a Mass Flow Sensor.

Table 2a. Mean (SD) age, height, BMI, z-scores according to GLI-2012 for FEV1, FVC and FEV1/FVC by stepwise exclusion of subjects with respiratory diseases, symptoms and smoking history according to category A-D[#] for persons aged 20-95 years representing the Tromsø, Hordaland and the HUNT Study

Age 20 – 95 years	Women							Men						
	n	Age	Height	BMI	z-FEV1	z-FVC	z-FEV1/FVC	n	Age	Height	BMI	z-FEV1	z-FVC	z-FEV1/FVC
Parent population ^A	8048	56.9	163.7	26.6	-0.19	0.04	-0.46	6572	56.7	177.0	27.1	-0.29	-0.06	-0.42
		(15.4)	(6.5)	(4.7)	(1.13)	(0.99)	(0.92)		(15.1)	(6.9)	(3.8)	(1.11)	(0.99)	(1.03)
Subjects without cardinal symptoms ^B	3357	54.9	164.3	25.7	0.06	0.22	-0.33	2907	55.3	177.5	26.7	-0.02	0.11	-0.23
		(14.9)	(6.2)	(4.2)	(1.02)	(0.94)	(0.82)		(14.6)	(6.7)	(3.6)	(0.99)	(0.93)	(0.88)
Never-smokers without cardinal symptoms ^C	1570	55.3	163.8	25.8	0.15	0.23	-0.21	1190	52.0	178.4	26.5	0.06	0.10	-0.09
		(16.3)	(6.3)	(4.4)	(0.98)	(0.92)	(0.79)		(15.1)	(6.6)	(3.3)	(0.93)	(0.90)	(0.82)
Never-smokers without respiratory symptoms ^D	1403	55.6	163.6	25.8	0.17	0.25	-0.20	1035	52.3	178.2	26.5	0.08	0.12	-0.09
		(16.3)	(6.3)	(4.3)	(0.98)	(0.91)	(0.78)		(15.3)	(6.5)	(3.3)	(0.92)	(0.87)	(0.82)

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Table 2b. Mean (SD) age, height, BMI, z-scores according to GLI-2012 for FEV1, FVC and FEV1/FVC by stepwise exclusion of subjects with respiratory diseases, symptoms and smoking history according to category A-D# for persons aged 12-19 years representing Young-HUNT Study

Age 12-19 years	Girls							Boys						
	n	Age	Height		z-FEV1	z-FVC	Z- FEV1/FVC	n	Age	Height		z-FEV1	z-FVC	Z- FEV1/FVC
Parent population ^A	7711	16.1 (1.8)	165.4 (6.3)		0.09 (1.02)	0.05 (0.98)	-0.29 (0.85)	7904	16.0 (1.8)	174.4 (9.5)		-0.01 (1.05)	0.05 (1.06)	-0.11 (0.96)
Subjects without cardinal symptoms ^B	5767	16.0 (1.8)	165.5 (6.3)		-0.08 (1.02)	0.03 (0.98)	-0.25 (0.85)	5850	16.0 (1.7)	174.6 (9.4)		0.02 (1.04)	0.03 (1.06)	-0.03 (0.94)
Never-smokers without cardinal symptoms ^C	5032	15.9 (1.8)	165.4 (6.3)		-0.08 (1.01)	0.03 (0.98)	-0.23 (0.84)	5236	15.9 (1.7)	174.3 (9.6)		0.02 (1.05)	0.02 (1.06)	-0.02 (0.94)
Never-smokers without respiratory symptoms ^D	4166	15.9 (1.8)	165.3 (6.4)		-0.07 (1.06)	0.03 (1.00)	-0.21 (0.83)	4559	15.9 (1.7)	174.1 (9.6)		0.02 (1.05)	-0.01 (1.06)	-0.02 (0.94)

^A parent population randomly selected persons, ^B persons without obstructive lung disease, BMRC 0, no wheezing and no chronic cough

^C Never-smokers, ^D Never-smokers without any respiratory symptoms. Ref: Johannessen et al, Thorax 2007;62:792-798

Table 3 Median, 5th and 95th percentile and percent below lower limit of normal (LLN) for z-FEV₁, z-FVC and z-FEV₁/FVC stratified by age and sex in the Norwegian reference sample.

Sex	Index	Adolescents < 20 years					Adults > 20 years				
		N	50%	5%	95%	% < LLN ^{&}	N	50%	5%	95%	% < LLN ^{&}
Males	FEV ₁	4559	0	-1.61	1.74	4.58	1035	0.06	-1.35	1.64	2.41
	FVC		-0.1	-1.69	1.76	5.52		0.11	-1.3	1.54	1.83
	FEV ₁ /FVC		0.06	-1.68	1.36	5.31		-0.02	-1.49	1.22	3.29
Females	FEV ₁	4166	-0.04	-1.78	1.57	6.12	1403	0.15	-1.4	1.79	3.14
	FVC		0.03	-1.60	1.61	4.60		0.25	-1.18	1.76	1.71
	FEV ₁ /FVC		-0.11	-1.72	0.98	5.83		-0.17	-1.51	0.98	3.71

& According to GLI-2012

Table 4 Prevalence of subjects identified as obstructive by GLI-2012, Nor-2015 (FEV₁/FVC < LLN) and FEV₁/FVC < 0.70) by sex in in the weighted sample (N= 50,580) representing all HUNT3 participants, and among these the prevalence of symptoms and diagnosis of obstructive lung disease, and cardiovascular diseases.

Self-reported symptoms and diseases	Males				Females			
	All	Obstructive according to			All	Obstructive according to		
		GLI-2012	Nor-2015	FEV ₁ /FVC < 0.70		GLI-2012	Nor-2015	FEV ₁ /FVC < 0.70
N	22490	1569	1658	2648	28090	1954	1692	2346
Percent obstructive		7.0	7.4	11.8		7.0	6.0	8.4
Wheezing or dyspnea last 12 months	11.2	36.1	37.3	29.6	11.9	32.0	37.2	32.7
Daily cough with phlegm	12.1	30.2	29.9	25.1	9.0	22.2	23.3	23.8
Modified MRC [#] > 2	2.4	14.4	15.8	10.9	2.6	13.0	15.0	13.4
Use of asthma medication last 5 years	9.4	38.2	39.1	29.8	11.1	34.2	40.1	33.5
Use of asthma medication last 12 months	7.0	33.7	35.3	25.4	8.7	29.3	34.1	30.2
Ever asthma	11.4	33.5	33.4	26.4	12.6	30.5	33.7	29.1
Doctor diagnosis of asthma	9.4	31.4	32.3	23.7	11.0	26.8	29.2	26.6
Ever COPD, emphysema or chronic bronchitis	3.3	20.0	21.6	15.3	3.3	16.8	20.7	17.0
Doctor diagnosis of COPD, emphysema or chronic bronchitis	2.9	18.1	20.8	13.5	2.8	16.2	19.6	16.6
Ever myocardial infarction	4.2	5.4	7.1	7.9	1.1	2.8	3.5	3.0
Ever stroke	2.6	3.6	4.3	4.8	2.2	1.4	1.8	3.3

[#] Modified British Medical Research Council Dyspnea Score

Table 5 Unadjusted and age adjusted risk (OR and 95% CI) for affirmative answers to questions on symptoms, use of medication and diseases for persons with FEV₁/FVC < LLN (1953 females and 1552 males) compared to FEV₁/FVC < 0.7 and ≥ LLN (793 females and 1264 males).

Self-reported symptoms, use of medications and diseases	OR	Males		OR	Females	
		Age adjusted OR	95%CI		Age adjusted OR	95%CI
Wheezing or dyspnea last 12 months	2.4	3.6	(3.0-4.4)	1.4	2.6	(2.1-3.3)
Daily cough with phlegm	2.2	3.1	(2.5-3.9)	1.1	1.3	(1.1-1.7)
Modified MRC > 2	3.1	5.6	(4.0-8.1)	1.9	4.1	(2.7-6.1)
Use of asthma medication last 5 years	3.1	4.8	(3.9-5.9)	1.7	3.2	(2.5-4.0)
Use of asthma medication last 12 months	3.4	5.7	(4.4-7.3)	1.6	3.2	(2.4-4.2)
Ever asthma	2.8	2.9	(2.4-3.5)	1.3	2.3	(1.8-2.9)
Doctor diagnosis of asthma	2.9	3.5	(2.7-4.6)	1.4	2.2	(1.6-2.9)
Ever COPD, emphysema or chronic bronchitis	3.2	6.0	(4.6-7.8)	1.8	4.2	(3.1-5.6)
Doctor diagnosis of COPD, emphysema or chronic bronchitis	3.6	6.8	(4.8-9.5)	2.0	4.3	(3.0-6.3)
Ever myocardial infarction	0.4	0.7	(0.5-1.0)	1.4	4.5	(2.4-8.3)
Ever stroke	0.6	1.3	(0.9-1.8)	0.2	0.7	(0.5-1.3)

Figure legends

Figure 1

Scatter of z-scores and median z-scores (solid lines) of FEV₁, FVC and FEV₁/FVC in males and females by age, height and study site. Dashed lines represent the 5th and 95th centiles.

Figure 2

Bland Altman Plots showing difference by mean predicted lung indices by each of Zapletal, ECSC, Nor-2015 and GLI-2012 reference values in males and females.

Supplement figure 1

Flowchart: Background for weighting by probability for been invited to spirometry in HUNT3 according to different criteria.

Among adults, persons were invited to spirometry if:

1. They previously had participated in the YoungHUNT1 study (1995-97).
2. They gave affirmative answers in the main questionnaire to: ever having had asthma or COPD, use of medication for asthma or COPD during the last 5 years, or reported attacks of wheezing or breathlessness during the last 12 months.
3. They were included in a 10% random sample of all participants at HUNT3.

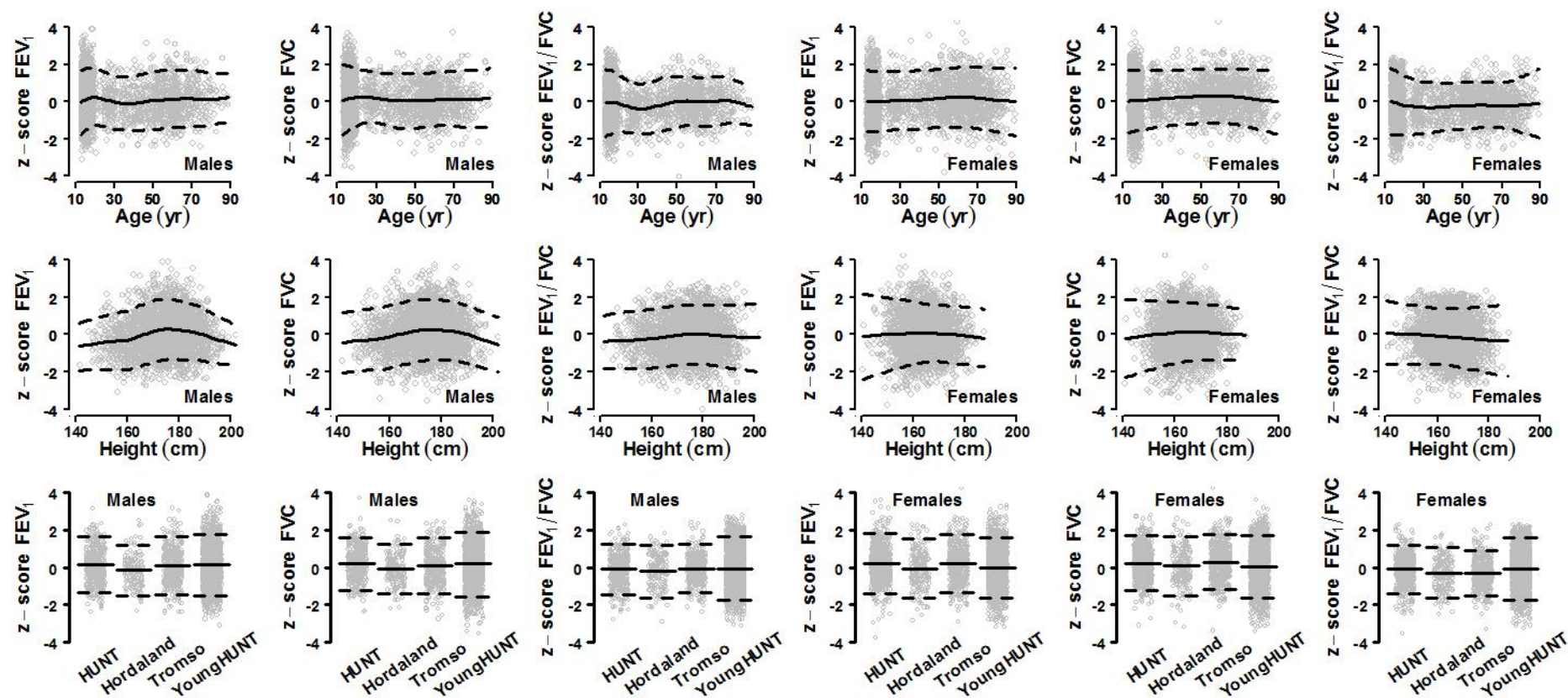
By weighting with the inverse probability of having been invited to spirometry, means of continuous variables and frequency of categorical data could be estimated for all participants of HUNT3, independent on participation in spirometry or not.

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Supplement figure 2

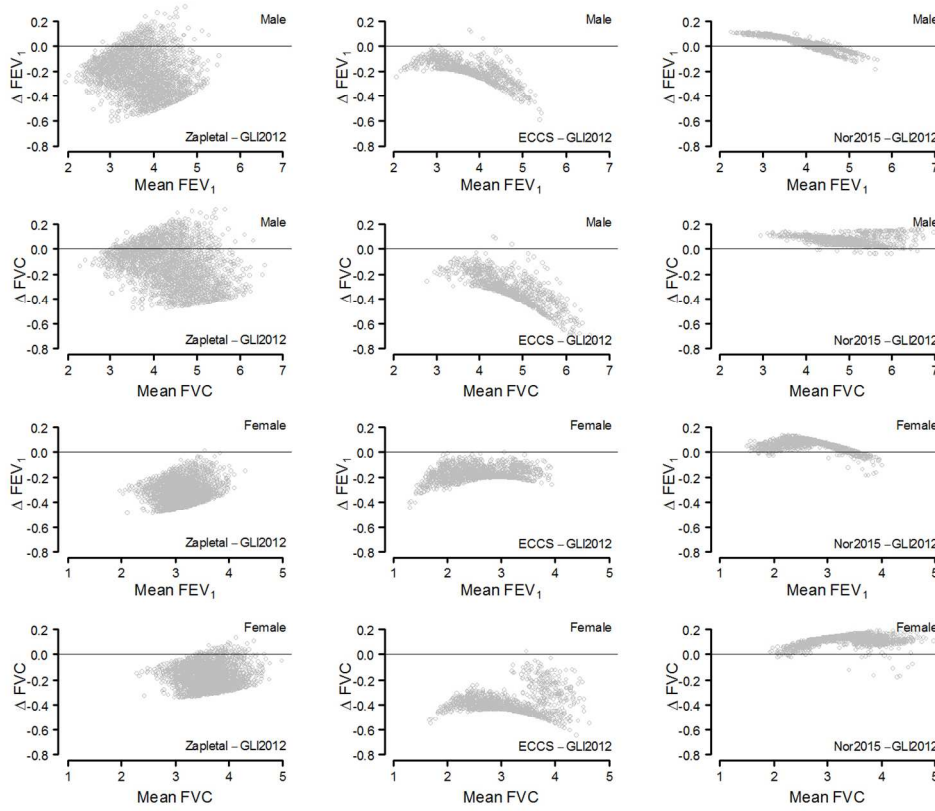
Bland Altman Plots showing difference by mean predicted lung indices by each of Gulsvik, Langhammer, Johannessen and GLI-2012 reference values in males and females.

Figure 1



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Bland Altman Plots showing difference by mean predicted lung indices by each of Zapletal, ECSC, Nor-2015 and GLI-2012 in males and females.

127x105mm (300 x 300 DPI)

HUNT3 Invited persons age 20-100 years: n=93,860
 Participated: n=50,807 (54.1%)

Invited to spirometry by criteria

Previous participants in
 YoungHUNT1 1995-97 (ALL)
 Invited 1428

Self-reported diagnosis or symptoms of OLD
 Invited 11,424 excluding random sample
 Invited 12,875 including from random sample

10 % random sample of
 all participants
 Invited 5067 of 36,504

Participated and
 acceptable spirometry
 n=728 (51.0%)

Participated and
 acceptable
 spirometry
 n= 8417 (73.7%)

Participated and
 acceptable spirometry
 n= 3574 (70.5%)

Diagnosis or
 symptoms of
 OLD n=18

Diagnosis or
 symptoms of
 OLD n=1094

Without symptoms or
 diagnosis of OLD
 Participated n=710

Diagnosis or symptoms of OLD
 Participated n=9529

Random sample excluded
 symptoms or diagnosis of OLD
 Participated n=2480

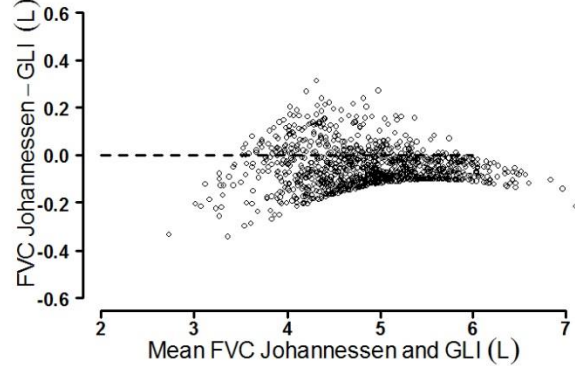
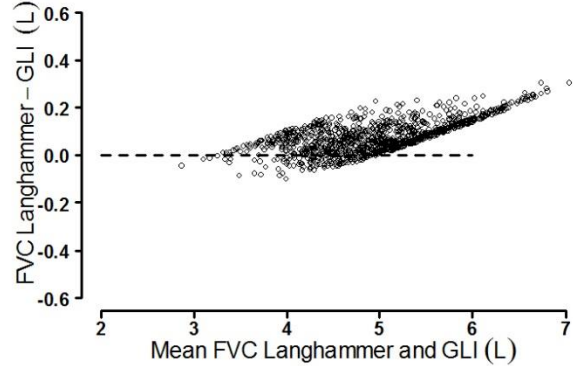
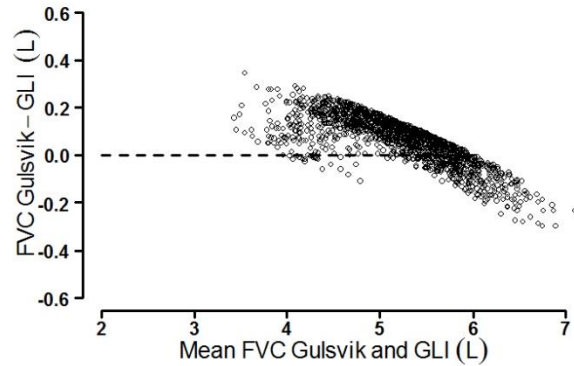
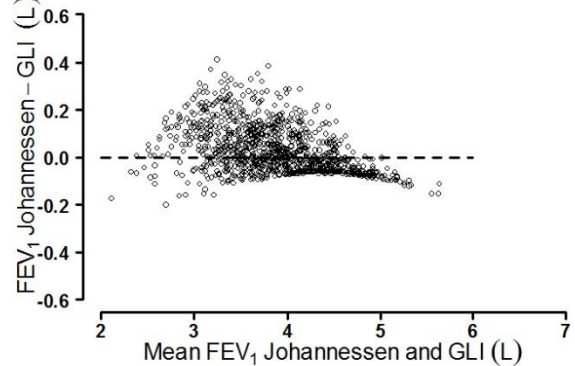
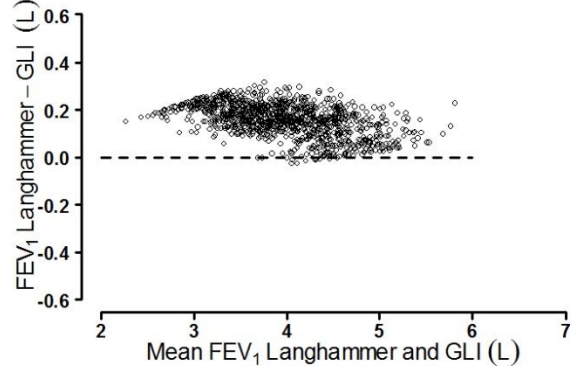
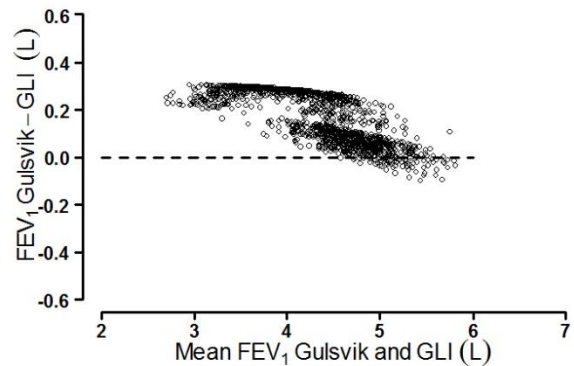
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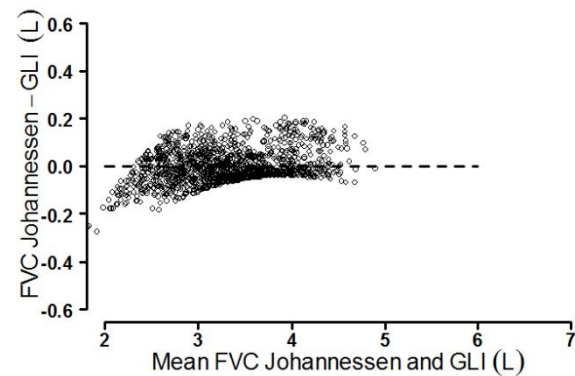
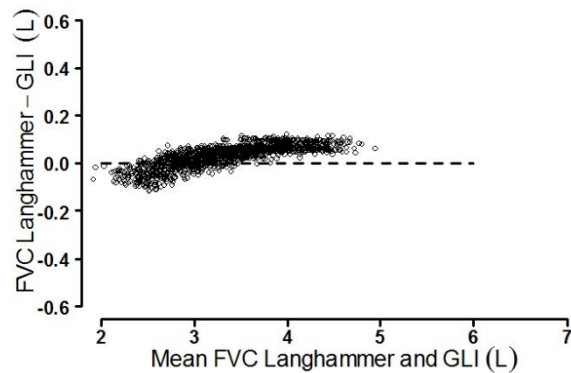
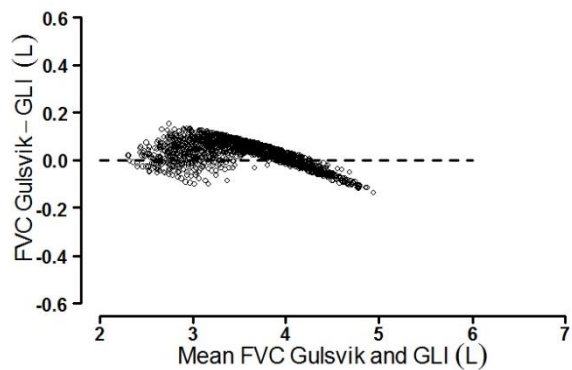
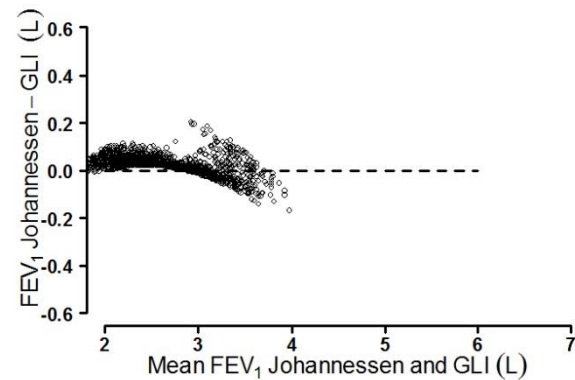
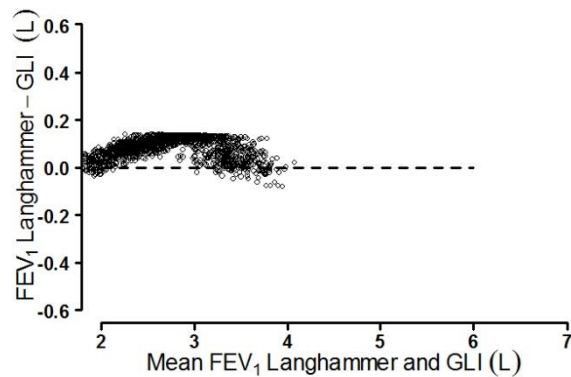
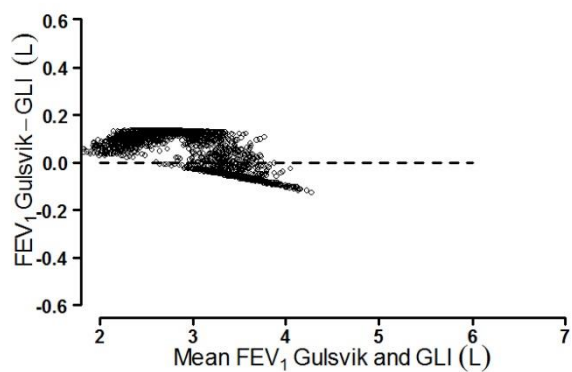
Bland Altman Plot males



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Bland Altman Plots females



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Supplement table S1. Stepwise exclusion of subjects with respiratory diseases, symptoms and smoking history according to category A-D[#]. Mean (SD) age, height, BMI, z-scores according to GLI-2012 for FEV1, FVC and FEV1/FVC for persons aged 20-95 years by study site.

	Women							Men						
	n	Age	Height	BMI	z-FEV1	z-FVC	z- FEV1/FVC	n	Age	Height	BMI	z-FEV1	z-FVC	z- FEV1/FVC
Hordaland														
Parent population (A)	1278	56.1 (15.1)	164.5 (6.5)	25.9 (5.2)	-0.48 (1.11)	-0.19 (1.03)	-0.56 (0.94)	1200	54.8 (14.3)	177.6 (6.9)	26.5 (4.0)	-0.59 (1.10)	-0.28 (0.99)	-0.58 (1.05)
Subjects without cardinal symptoms (B)	621	53.7 (14.2)	165.1 (6.1)	25.3 (4.7)	-0.18 (0.99)	0.04 (0.96)	-0.43 (0.85)	612	53.7 (13.7)	178.2 (6.9)	26.3 (4.0)	-0.25 (0.96)	-0.07 (0.90)	-0.33 (0.92)
Never-smokers without cardinal symptoms (C)	322	55.8 (15.2)	164.7 (6.2)	25.5 (4.7)	-0.08 (0.99)	0.08 (0.97)	-0.32 (0.84)	253	50.8 (13.6)	179.5 (6.6)	26.2 (3.5)	-0.17 (0.83)	-0.07 (0.83)	-0.18 (0.86)
Never-smokers without respiratory symptoms D	218	56.4 (14.7)	164.2 (6.3)	25.1 (4.8)	-0.04 (0.97)	0.09 (0.97)	-0.27 (0.82)	176	51.6 (14.1)	179.4 (6.7)	26.0 (3.5)	-0.15 (0.82)	-0.06 (0.81)	-0.18 (0.86)
TROMSØ														
Parent population (A)	3668	63.7 (9.3)	162.5 (6.4)	26.8 (4.6)	-0.24 (1.13)	0.04 (0.99)	-0.54 (0.92)	2769	63.7 (9.1)	175.7 (6.7)	27.4 (3.7)	-0.33 (1.11)	-0.08 (0.99)	-0.43 (1.05)
Subjects without cardinal symptoms (B)	1351	61.5 (8.9)	163.3 (6.3)	25.5 (3.8)	0.08 (0.99)	0.29 (0.92)	-0.42 (0.79)	1145	62.3 (8.7)	176.3 (6.4)	26.7 (3.2)	-0.04 (0.98)	0.10 (0.95)	-0.24 (0.87)
Never-smokers without cardinal symptoms (C)	585	62.8 (9.5)	162.7 (6.2)	25.7 (4.0)	0.20 (0.94)	0.32 (0.90)	-0.28 (0.74)	433	60.9 (8.6)	176.7 (6.1)	26.4 (2.9)	0.10 (0.95)	0.12 (0.93)	-0.04 (0.79)
Never-smokers without respiratory symptoms D	571	62.9 (9.5)	162.7 (6.2)	25.7 (4.0)	0.20 (0.95)	0.32 (0.91)	-0.28 (0.74)	404	60.7 (8.5)	176.7 (6.1)	26.5 (2.9)	0.09 (0.94)	0.10 (0.91)	-0.04 (0.78)
HUNT														
Parent population (A) (random sample)	3105	49.1 (17.5)	164.8 (6.4)	26.5 (4.7)	-0.02 (1.11)	0.12 (0.97)	-0.31 (0.89)	2604	50.1 (17.3)	177.9 (6.9)	27.7 (3.8)	-0.12 (1.11)	0.06 (0.98)	-0.33 (0.99)
Subjects without cardinal symptoms (B)	1386	49.0 (17.2)	164.9 (6.1)	26.1 (4.4)	0.15 (1.04)	0.23 (0.93)	-0.21 (0.83)	1150	49.3 (16.7)	178.3 (6.8)	26.9 (3.6)	0.13 (0.98)	0.22 (0.93)	-0.17 (0.86)
Never-smokers without cardinal symptoms (C)	663	48.6 (18.1)	164.6 (6.2)	26.1 (4.5)	0.21 (1.00)	0.23 (0.89)	-0.10 (0.79)	504	45.9 (16.4)	178.9 (6.7)	26.8 (3.7)	0.15 (0.95)	0.18 (0.89)	-0.08 (0.83)
Never-smokers without respiratory symptoms D	614	49.0 (17.5)	164.5 (6.2)	26.1 (4.2)	0.22 (0.99)	0.24 (0.88)	-0.10 (0.79)	455	45.3 (15.4)	179.0 (6.4)	26.9 (3.6)	0.16 (0.92)	0.20 (0.85)	-0.09 (0.83)

Category A parent population randomly selected persons

Category B persons without obstructive lung disease, BMRC 0, no wheezing and no chronic cough

Category C Never-smokers

Category D Never-smokers without any respiratory symptoms. Ref: Johannessen et al, Thorax 2007;62:792-798

Supplement table S2

Comparisons of prevalence estimates based on the main questionnaire in HUNT3 answered by 50.807 persons and sample weighted by the probability for being selected to spirometry in HUNT3.

Self-reported	Males		Female	
	Main	Weighted	Main	Weighted
	questionnaire	sample	questionnaire	sample
	HUNT3		HUNT3	
Wheezing or dyspnea last 12 m	12.3	11.2	12.4	11.7
Use of asthma medication last 5 yr	9.6	9.4	11.1	11.1
Ever asthma	11.2	11.4	12.2	12.6
Ever COPD	3.5	3.3	3.4	3.3
Ever myocardial infarction	5.2	4.2	1.6	1.1
Ever stroke	3.0	2.6	2.2	2.2