Chapter 6

Reproducibility of carotid intima-media thickness measurement in overweight and obese adults: the NEO study

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ABSTRACT

Background and aims

The carotid intima-media thickness (cIMT) is a marker for subclinical atherosclerosis and is strongly associated with future cardiovascular disease. The reproducibility of the cIMT is unknown in a population consisting exclusively of overweight individuals. The aim of this study was to evaluate the reproducibility of the cIMT measurement in overweight and obese adults.

Methods and results

Paired cIMT scans were performed in a random sample in the NEO (Netherlands Epidemiology of Obesity) study, a population based cohort study of individuals aged 45-65 years with a Body Mass Index (BMI) ≥27 kg/m^2. The cIMT was measured by ultrasound in the far wall of both common carotid arteries. The 169 participants had a mean (SD) age of 56 (6) years, mean BMI of 31.4 (4.0) kg/m^2, and 54% men. The mean cIMT was 0.659 (0.071) mm. The 76 intra-observer measurements had a mean absolute cIMT difference of 0.043 mm (0.033), coefficient of variation (CV) of 5.8% and intra-class correlation coefficient (ICC) of 0.74 (95% CI: 0.62, 0.83). The 93 inter-observer measurements had a mean absolute difference of 0.064 mm (0.054), CV of 9.0% and ICC of 0.49 (95% CI: 0.33, 0.63). The cIMT reproducibility was not associated with age, sex, BMI, waist circumference, blood pressure, glucose, total cholesterol, high density or low density lipoprotein concentrations. There was a weak association between cIMT and inter-observer reproducibility.

Conclusion

This reproducibility study showed a good intra-observer (CV 5.8%) and a fair inter-observer agreement (CV 9.0%) of the cIMT measurement in overweight and obese adults.

INTRODUCTION

Overt cardiovascular disease (CVD) is the end stage of atherosclerosis progression [204]. Atherosclerosis starts with endothelial cell dysfunction. In the presence of oxidized low density lipoprotein (LDL), inflammation and smooth muscle cell proliferation, the intima and media layer of the arterial wall thickens gradually. Eventually an atherosclerotic plaque can be formed. This progression of vascular abnormalities remains subclinical until the plaque narrows the arterial lumen considerably or when the plaque ruptures and causes thrombus formation [204].

The carotid intima-media thickness (cIMT) can be measured by ultrasound. It corresponds with histology of the arterial vessel wall and the cIMT is a marker for subclinical atherosclerosis [87]. It is also strongly associated with future risk of CVD [88]. Therefore assessment of cIMT is widely used in large-scale observational and experimental research. Furthermore, it is recently recommended by the Society of Atherosclerosis Imaging and Prevention to use cIMT measurements to reclassify individuals with an intermediate CVD risk (i.e.10-year absolute CHD risk between 10% and 20%), because many cardiovascular events still occur in individuals who are not in high risk groups [205].

Precision of the cIMT measurement is crucial since observed variance of cIMT should reflect 'true differences' between individuals and not inadequate measurement performance. Poor reproducibility of cIMT measurement could lead to misclassification, insufficient sample sizes and diluted effect estimates. The reproducibility of the cIMT measurement varies according to the measured artery, equipment used, number of assessors and study population [90]. In overweight individuals excess fat in the neck region may render cIMT more difficult to assess. The prevalence of overweight increases rapidly and many individuals in intermediate CVD risk groups are overweight [206] and could thus be candidates for cIMT risk stratification. However, prevailing cIMT measurements may not be valid in overweight individuals and need therefore to be validated.

The aim of this study was to examine the reproducibility of the cIMT measurement in the common carotid artery (CCA) in overweight and obese individuals and to study the effects of body mass index (BMI) and other cardiovascular risk factors on the reproducibility of the cIMT measurement.

METHODS

Study population

Men and women aged between 45 and 65 years with a self-reported BMI of 27 kg/m^2 or higher from Leiden and surroundings were eligible to participate in the NEO (Netherlands Epidemiology of Obesity) study. Exclusion criteria were a life expectancy of less than 6 months, severe psychiatric disease and insufficient knowledge of the Dutch language. The study was approved

by the medical ethics committee of the Leiden University Medical Center (LUMC) and all participants gave written informed consent.

Study design

The NEO study is a population based prospective cohort study in overweight and obese individuals that started in September 2008. Initially, participants were recruited by a research network of general practitioners in the area of Leiden. This research network consists of 82 practices and covers a population of 250,000 subjects. General practitioners sent invitations to participate to their patients aged between 45 and 65 years. Eligible men and women (i.e. BMI of 27 kg/m^2 or higher) were invited to contact the NEO study center by telephone or by completing a web-form. A reminder was sent after two weeks. In addition, participants were recruited through advertisements in local newspapers. At home, eligible participants collected a 24- or 12-hour sample of urine and completed a questionnaire about demographic and clinical data such as smoking and disease history of CVD and diabetes. Then, participants visited the NEO study site in the morning for several baseline measurements including anthropometric measurements, blood sampling and a cIMT measurement.

Height and weight were measured without shoes and one kilogram was subtracted from the weight for clothing. BMI was calculated by dividing weight in kilograms by the height in meters squared. Waist circumference was measured between the border of the lower costal margin and the iliac crest with the precision of 0.1 centimeters. Blood samples were taken after an overnight fast of at least 10 hours. Serum levels of glucose, total cholesterol and high density lipoprotein (HDL) were determined by using standard enzymatic methods (*Roche Modular Analytics P800, Almere, The Netherlands*) in the central clinical chemistry laboratory of the LUMC. We calculated low density lipoprotein (LDL) concentration with the Friedewald formula (LDL= total cholesterol – (HDL + 0.48 x triglycerides)) [207]. Brachial blood pressure was measured in seated position on the right arm using a validated automatic oscillometric device (*OMRON, Model M10-IT, Omron Health Care Inc, IL, USA*). Blood pressure was measured 3 times with 5 minutes rest between consecutive measurements. Blood pressure was calculated as the mean systolic and diastolic blood pressure of these 3 measurements.

We performed paired scans of the cIMT in a random sample of participants at the baseline of the study. Seven sonographers took scans from January 19, 2009 to February 27, 2009 and from July 6, 2009 to September 30, 2009. In these periods, participants were scanned twice by two sonographers during 10 consecutive working days. During another 10 consecutive working days participants were scanned twice by the same sonographer. We term paired scans assessed by the same sonographer as intra-observer measurements and paired scans assessed by two sonographers as inter-observer measurements. We asked sonographers with less than 5 paired intra-observer or inter-observer measurements to perform extra scans. The intra-observer measurements were performed with at least a 1 hour interval between paired scans. Between paired scans participants were allowed to walk. Sonographers were blinded for the scan of

the other sonographer. All sonographers were right-handed research nurses who recently had been trained to measure cIMT by an experienced sonographer according to standardized procedures [208].

Carotid intima-media thickness measurement

The cIMT was measured in the far wall of the left and right CCA along a 15 mm long section 10 mm proximal of the bifurcation in recumbent position. A 7.5-10 MHz linear-array transducer (*Art.Lab version 2.1, Esaote, Maastricht, The Netherlands*) in B-mode setting was used to visualize the distal CCA and an automatic wall track system was used to detect the lumen-intima and media-adventitia boundaries. The cIMT was measured in three predefined angles per side (180,135 and 90 degrees for the right CCA and 180, 225 and 270 degrees for the left CCA) and per angle the cIMT was measured during 6 consecutive complete heart cycles. We calculated the mean cIMT for each participant (referred to as cIMT) by averaging all 36 cIMT measurements within each individual.

Statistical analyses

Baseline characteristics of the participants were expressed in mean (SD) or as number (%). We verified whether the random sample was representative for the NEO study population by comparison of its characteristics with the non-selected participants in the NEO study. Differences were tested by student t-tests and chi-squared tests where appropriate.

To study agreement within and between sonographers we constructed Bland-Altman plots [209] and calculated 95% limits of agreement (LA), intraclass correlation coefficients (ICCs) [210] and coefficients of variation (CVs) [211] for intra-observer and inter-observer measurements separately. For the Bland-Altman plots we calculated the mean cIMT of 2 paired measurements and the difference between 2 paired cIMT measurements by subtracting the second measurement from the first measurement. The ICC explains how much of the total variance between measurements is caused by true inter-subject variability. An ICC of one represents perfect agreement and ICC of zero implies no agreement at all. The CV expresses the standard error between paired measurements as a percentage of the sample mean, where a CV of 0% equals perfect agreement and a CV of 100% signifies no agreement at all.
We calculated the ICC and CV for the intra-observer measurements using the formulas:

$$ICC_{intra} = (\sigma_s^2 + \sigma_o^2) / (\sigma_s^2 + \sigma_o^2 + \sigma_e^2) \quad [1]$$

$$CV_{intra} = 100\% \times (\sigma_e / \text{mean cIMT}) \quad [2]$$

where σ_s^2 is subject variance, σ_o^2 is inter-observer variance, σ_e^2 is error variance. We calculated the ICC and CV for the inter-observer measurements using the formulas:

$$ICC_{inter} = \sigma_s^2 / (\sigma_s^2 + \sigma_o^2 + \sigma_e^2) \quad [3]$$

$$CV_{inter} = 100\% \times ((\sigma_o + \sigma_e) / \text{mean cIMT}) \quad [4]$$

All variance components were calculated by restricted maximum likelihood estimation (REML). We obtained 95% confidence intervals (CIs) for the ICCs by using the delta method [212].

Subsequently, we calculated absolute differences between 2 measurements by subtracting the lowest cIMT measurement from the highest cIMT measurement, to examine whether cIMT reproducibility is affected by the cIMT itself, age, sex, disease history of CVD and type 2 diabetes, BMI, waist circumference or cardiovascular risk factors such as smoking, systolic blood pressure, diastolic blood pressure, fasting glucose, total cholesterol, HDL and LDL concentration. Disease history of CVD and type 2 diabetes were based on self-report in the questionnaire. Participants who used oral hypoglycemic medication or insulin were also classified as type 2 diabetics. CVD was defined as having a disease history of myocardial infarction, cerebrovascular disease, congestive heart failure, angina or peripheral artery disease. We constructed scatter plots and used univariable linear regression to calculate regression coefficients (β). We calculated coefficients for the association between the mean of 2 cIMT measurements and the absolute difference between 2 measurements. These coefficients were calculated for a 0.1 mm increase in mean cIMT. Coefficients for the other variables were calculated for a one unit increase.

Analyses were performed with PASW statistics release 17.0 (*SPSS Inc, Chicago, IL, USA*) and 95% confidence intervals for the ICCs were calculated with SAS version 9.2 (*SAS Institute Inc, Cary, NC, USA*).

RESULTS

At November 20, 2009, 1,405 participants were included in the NEO study. From January 19, 2009 to February 27, 2009 and from July 6, 2009 to September 30, 2009, 169 participants were randomly selected for paired cIMT scans. Selected participants had a mean age of 56 years (SD 6), 54% was male, 46% had overweight, 54% was obese, 5% had a history of overt CVD and 7% had known type 2 diabetes. The mean cIMT was 0.659 mm (SD 0.071, range 0.494 to 0.895, interquartile range 0.612 to 0.703).

At baseline, there were no differences between characteristics of the randomly selected participants and the other participants in the NEO study (**Table 1**).

Of the 169 participants, 76 participants were scanned twice by the same sonographer. Ninety-three participants were scanned twice by two different sonographers.

The mean difference for the intra-observer measurement was -0.009 mm (SD 0.054, 95% LA -0.114 mm to 0.097 mm, **Figure 1**, Panel A) and the mean absolute difference was 0.043 mm (SD 0.033). Sixty-nine (91%) intra-observer measurements had an absolute cIMT difference between paired measurements of less than 0.100 mm. The intra-observer ICC was 0.74 (95% CI 0.62 to 0.83) and the CV was 5.8% (**Appendix Table**). The inter-observer measurements had a

Table 1. Baseline characteristics of the random sample and the non-selected participants in the NEO study

Characteristics	Sample (n=169)	NEO study (n=1236)	Mean difference (95% CI)
Age	55.5 (6.0)	56.2 (5.7)	-0.7 (-1.6, 0.3)
Sex (n, % men)	91 (54)	599 (48)	5 (-3, 13)[a]
BMI (kg/m^2)	31.4 (4.0)	31.0 (3.9)	0.5 (-0.2,1.1)
Waist circumference (cm)			
Men	109 (8)	109 (9)	0.4 (-1.5, 2.4)
Women	103 (11)	103 (11)	0.6 (-2.0, 3.2)
Disease history			
CVD	9 (5)	99 (8)	-2 (-6, 2)[a]
Type 2 diabetes	12 (7)	99 (8)	-1 (-5, 3) [a]
Current smoking	27 (16)	210 (17)	-1 (-7, 5) [a]
Systolic blood pressure (mmHg)	134 (14)	133 (18)	0.6 (-2.2, 3.4)
Diastolic blood pressure (mmHg)	86 (9)	85 (11)	0.5 (-1.2, 2.2)
Glucose (mmol/l)	5.4 (1.4)	5.4 (1.2)	0.1 (-0.1, 0.3)
Total cholesterol (mmol/l)	5.6 (1.1)	5.7 (1.1)	-0.1 (-0.3, 0.0)
LDL (mmol/l)	3.5 (1.0)	3.7 (1.0)	-0.1 (-0.3, 0.0)
HDL (mmol/l)	1.34 (0.41)	1.33 (0.37)	0.01 (-0.05, 0.08)
cIMT (mm)	0.659 (0.071)	0.665 (0.085)	-0.007 (-0.020, 0.007)

The NEO study population consisted of individuals aged between 45 and 65 years and with a BMI ≥ 27 kg/m^2. Data are shown as mean (SD) or number (%) unless specified otherwise.

NEO, Netherlands Epidemiology of Obesity; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease, consisting of myocardial infarction, cerebrovascular disease, congestive heart failure, angina and peripheral artery disease; HDL, high density lipoprotein; LDL: low density lipoprotein; cIMT, carotid intima-media thickness

[a]Mean differences between the random sample and non-selected participants are shown in percentages.

mean difference of 0.000 mm (SD 0.084, 95% LA -0.164 mm to 0.164 mm, **Figure 1**, Panel B) and the mean absolute difference was 0.064 mm (SD 0.054). Seventy-seven (83%) inter-observer measurements had an absolute cIMT difference between paired measurements of less than 0.100 mm. The inter-observer ICC was 0.49 (95% CI 0.33 to 0.63) and the CV was 9.0% (**Appendix Table**). **Figure 2** shows no association between absolute cIMT difference and mean cIMT in intra-observer measurements (Panel A) and a weak association in inter-observer measurements (Panel B).

There were no associations between the absolute cIMT and age, sex, history of overt CVD or known type 2 diabetes, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, LDL, or HDL and absolute cIMT difference. There was a weak association between current smoking and absolute cIMT difference in inter-observer measurements (**Table 2**).

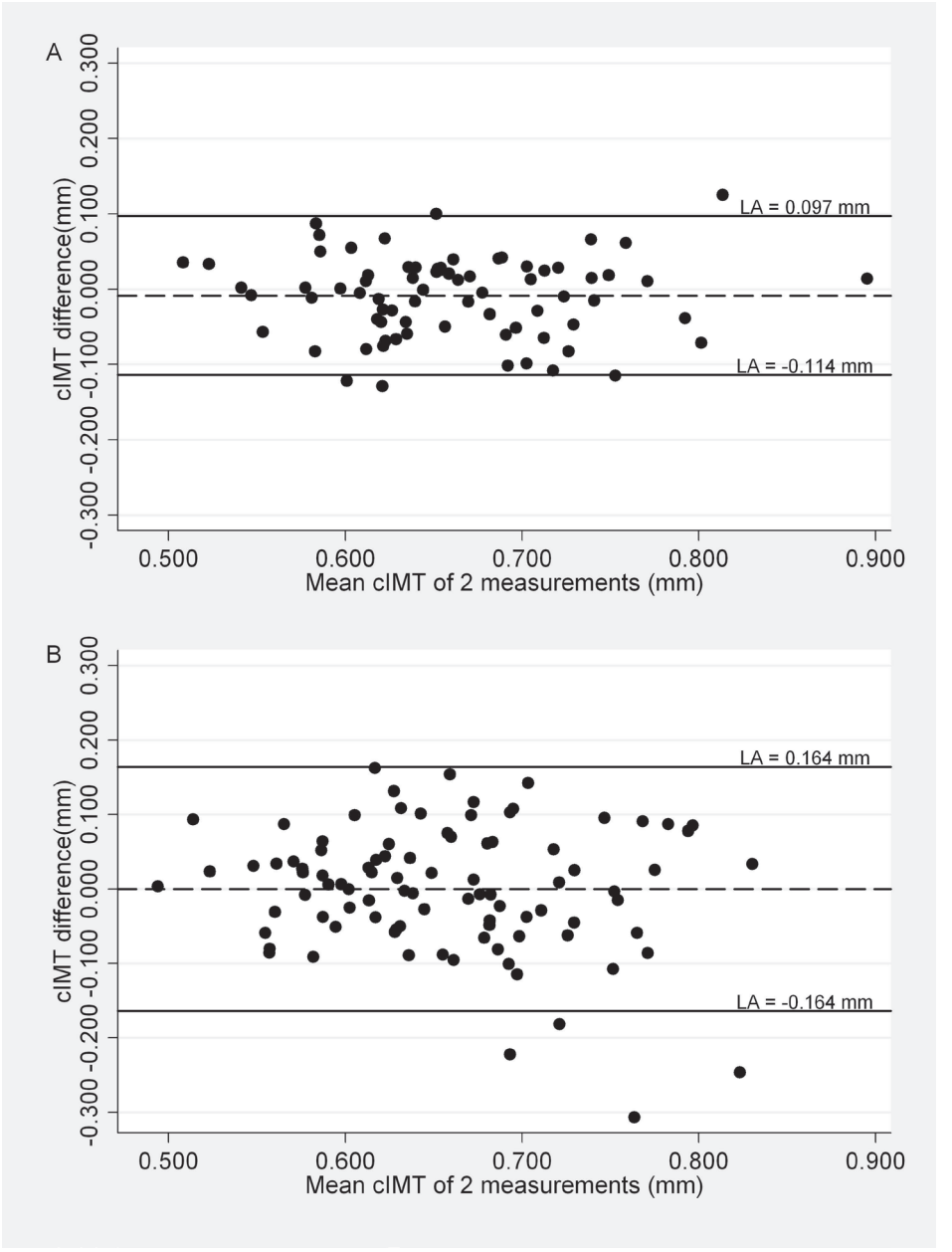

Figure 1. Bland-Altman plots for paired cIMT measurements in the NEO study
Panel A shows 76 intra-observer cIMT measurements and panel B shows 93 inter-observer cIMT measurements. The NEO study population consisted of individuals aged between 45 and 65 years and with a BMI ≥ 27 kg/m^2.
cIMT, carotid intima-media thickness; BMI, body mass index; LA, 95% limit of agreement

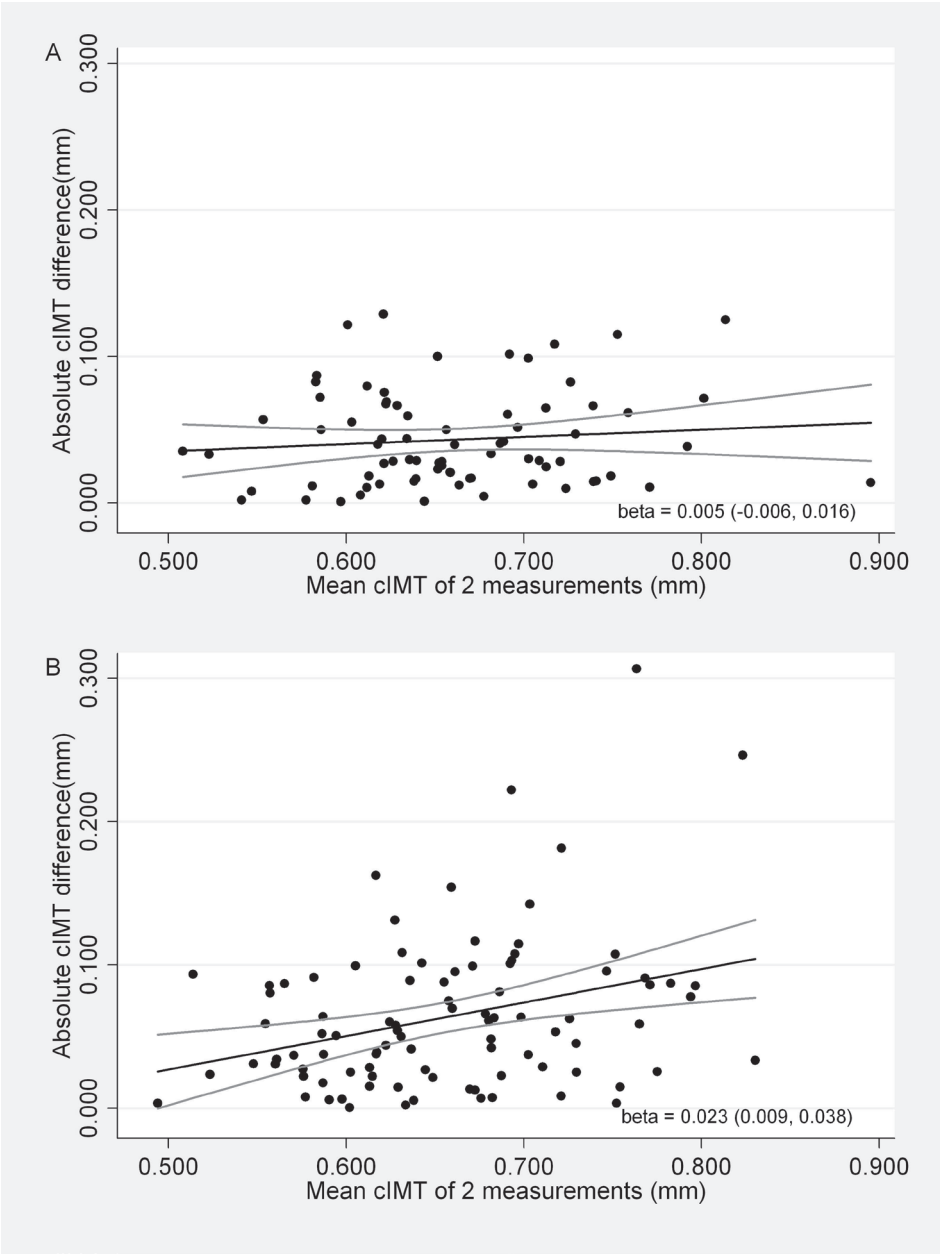

Figure 2. Scatter plots for the association between the mean cIMT of two measurements and absolute cIMT difference in the NEO study

Panel A shows the association for 76 intra-observer cIMT measurements and panel B for 93 inter-observer cIMT measurements. The NEO study population consisted of individuals aged between 45 and 65 years and with a BMI ≥ 27 kg/m^2.

cIMT, carotid intima-media thickness; β, mean change in absolute cIMT difference per 0.1 mm increase in mean cIMT with corresponding 95% confidence intervals

Table 2. Associations between cardiovascular risk factors and absolute cIMT difference for intra-observer and inter-observer measurements

Cardiovascular risk factor	Intra-observer measurements (n=76) β (95% CI)	Inter-observer measurements (n=93) β (95% CI)
Age (year)	-0.001 (-0.001, 0.002)	0.001 (0.000, 0.003)
Sex[a]	0.013 (-0.002, 0.028)	0.007 (-0.016, 0.029)
Disease history[b]		
CVD	0.013 (-0.026, 0.052)	-0.012 (-0.058, 0.034)
Type 2 diabetes	0.018 (-0.013, 0.048)	0.040 (-0.002, 0.048)
Current smoking[b]	0.000 (-0.021, 0.021)	0.036 (0.006, 0.065)
BMI (kg/m^2)	-0.002 (-0.004, 0.001)	-0.000 (-0.003, 0.002)
Waist circumference (cm)	0.000 (-0.001, 0.000)	0.000 (-0.001, 0.001)
Glucose (mmol/l)	0.003 (-0.002, 0.009)	0.007 (0.000, 0.014)
Systolic blood pressure (mmHg)	0.000 (0.000, 0.001)	0.000 (-0.001, 0.001)
Diastolic blood pressure (mmHg)	0.000 (-0.001, 0.001)	-0.001 (-0.003, 0.000)
Total cholesterol (mmol/l)	-0.007 (-0.016, 0.002)	0.000 (-0.009, 0.009)
LDL (mmol/l)	-0.008 (-0.019, 0.002)	-0.001 (-0.011, 0.009)
HDL (mmol/l)	-0.019 (-0.038, -0.001)	0.007 (-0.020, 0.034)

The NEO study population consisted of individuals aged between 45 and 65 years and with a BMI ≥ 27 kg/m^2. The regression coefficient represents the mean change in absolute cIMT difference per 1 unit increase in cardiovascular risk factor.

cIMT, carotid intima-media thickness; NEO, Netherlands Epidemiology of Obesity; BMI, body mass index; β, linear regression coefficient; CI, confidence interval; CVD, cardiovascular disease, consisting of myocardial infarction, cerebrovascular disease, congestive heart failure, angina and peripheral artery disease; LDL, low density lipoprotein; HDL, high density lipoprotein

[a] Female is reference category

[b] Participants without the disease or characteristic are the reference category

DISCUSSION

To our knowledge, this is the first study investigating the reproducibility of the cIMT measurement by ultrasound in a study population consisting exclusively of middle-aged adults with overweight or obesity. This reproducibility study showed a good intra-observer (CV 5.8%) and a fair inter-observer agreement (CV 9.0%) of the cIMT measurement by ultrasound in overweight and obese individuals. Importantly, cardiovascular risk factors did not affect cIMT reproducibility.

Interpretation of agreement is difficult and remains somewhat subjective, because absolute cut-off values defining good or poor agreement for 95% LA, ICCs, CVs and their combinations are lacking [213]. Hence, agreement should be interpreted by comparisons with reproducibility measures from other studies. We identified previous reproducibility studies on April 6, 2011 from a MEDLINE search and reference lists of retrieved articles. Our reproducibility measures of the cIMT measured in the far wall of the CCA are shown in **Table 3,** together with measures

Table 3. Measures of cIMT reproducibility in the NEO study and other population based studies

Name	Study characteristics		Intra-observer agreement					Inter-observer agreement				
	cIMT (mm)	BMI (kg/m^2)	n	LA[a] (mm)	MAD (mm)	ICC	CV (%)	n	LA[a] (mm)	MAD (mm)	ICC	CV (%)
NEO	0.659 (0.071)	31.4	76	±0.106	0.043	0.74	5.8	93	±0.164	0.064	0.49	9.0
ARIC [222, 223]	0.659 (0.325)	27.4[b]	33	-	-	0.65	10	33	-	-	0.53	7
CAPS [224]	0.72 (0.15)	27.1	35	-	0.03-0.06[c]	0.93	-	15	-	0.04-0.06[c]	0.97	-
CHS [225, 226]	0.73 (0.24)[d]	26.7[b]	54	-	0.13	-	-	107	-	0.18	-	-
LAAS [227]	0.741 (0.139)	28.6	38	-	0.027	-	4.2	38	-	0.041	-	6.1
Rotterdam [216]	0.75 (0.19)[e]	26.4	-	-	-	-	-	75	±0.176	-	0.65	-
Tromsø [215]	0.71 (0.18)	25.7	75	±0.12	0.06	-	5.9	75	±0.18	0.08	-	9.0

All studies measured the cIMT in the far wall of the CCA. Data are shown as mean (SD) unless specified otherwise. References are listed in the reference list.
cIMT, carotid intima-media thickness; CCA, common carotid artery; NEO, Netherlands Epidemiology of Obesity; BMI, body mass index; MAD, mean absolute difference; ICC, intraclass correlation coefficient; CV, coefficient of variation; NEO, Netherlands Epidemiology of Obesity; ARIC, Atherosclerosis Risk In Community; CAPS, Carotid Artery Progression Study; CHS, Cardiovascular Health Study; LAAS, Los Angeles Atherosclerosis Study

[a] LA: 95% limit of agreement, defined as ± 1.96 multiplied by the SD of the intra- or inter-observer difference

[b] Based on data of 13,145 participants (ARIC) or 5,843 participants (CHS)

[c] 95% interval of the mean absolute difference

[d] cIMT value for inter-observer agreement

[e] cIMT value for right CCA

from other cohort studies, not including studies with a sample size smaller than 30 and studies that did not assess agreement within or between sonographers.

By definition, the BMI in our study was higher than in other cIMT reproducibility studies. In overweight individuals, excess fat in the neck region may render cIMT to be more difficult to assess. Nevertheless, our intra-observer and inter-observer reproducibility measures are comparable with measures from other population based studies (**Table 3**). The Los Angeles Atherosclerosis Study found better reproducibility measures, but the cIMT scans in this study had been performed by only two different sonographers who had information regarding the anatomical position of the first cIMT scan. Despite similar inter-observer LA or mean absolute differences, our inter-observer ICC was lower than ICCs in other studies. In our study, there was less variation in cIMT between individuals, which may have resulted in a lower ICC (**Table 3**) [214].

In individuals with more advanced atherosclerosis, who may have an irregular cIMT, small differences in localization of cIMT measurement could lead to large differences between paired measurements. We found no association between the cIMT and reproducibility in intra-observer measurements and a weak association in inter-observer measurements. The Tromsø study found an association of cIMT with both intra- and inter-observer reproducibility [215]. The maximum cIMT in this study was higher than in our study (1.74 mm versus 0.895 mm), suggesting more advanced atherosclerosis. We found no association between BMI, waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, total cholesterol, HDL or LDL and cIMT reproducibility, except for smoking. We cannot explain the association between current smoking and cIMT reproducibility and it has not been described previously. We found that BMI did not affect cIMT reproducibility, but theoretically did can also be explained by little variability in BMI values. However, other population based studies that included persons with normal and high BMI's also found no associations between BMI or other cardiovascular risk factors and cIMT reproducibility [215, 216] Therefore, we are confident that the cIMT measurements in our population are valid.

Among strengths of this study are that the NEO study population consists exclusively of overweight and obese individuals and that detailed information on the presence of cardiovascular risk factors was available. Our random sample was representative for the NEO study population. Limitations may be that we cannot draw conclusions about the reproducibility of the cIMT measurement in individuals with a larger cIMT than included in the NEO study.

A meta-analysis showed that a cIMT difference of 0.1 mm increased CVD risk with 15 to 18 percent, and may therefore be considered clinically relevant [88]. In our study population, the mean absolute difference for intra- and inter-observer measurements was lower than 0.1 mm, but 9% of the intra-observer measurements and 17% of the inter-observer measurements had an absolute cIMT difference of 0.1 mm or higher. This means that a second cIMT measurement may estimate the individual CVD risk in 9% to 17% of this population 15% to 18% higher or lower than the first measurement. When cIMT is added to traditional CVD risk prediction mod-

els to reclassify individual CVD risk, this could lead to misclassification and possibly to over- or undertreatment. Studies that used cIMT to reclassify individual CVD risk have not addressed this problem [217-221]. As none of these studies reported formulas for CVD risk prediction with cIMT, we were not able to calculate the proportion of individuals whose CVD risk would be reclassified differently based on a second cIMT measurement. In addition to our results, scientific evidence for the additional value of cIMT in risk stratification is limited [217]. Nevertheless, the cIMT measurement can be validly used in large associational studies such as the NEO study in which measurement error can be overcome by a larger sample size. Measurement error can also be minimized by duplicate cIMT scans and by a single sonographer performing all the cIMT scans, although this may be too time-consuming and often not feasible in large epidemiological studies. We showed that even with 7 different sonographers a good intra-observer agreement and a fair inter-observer agreement can be achieved and conclude that measurement of the cIMT by ultrasonography is valid in a population of overweight and obese individuals.