

Online Supplementary Material

Association between snus use and lipid status in Swedish men

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Table of contents

Supplementary Text 1. Details of parametric model assumptions.....	1
Supplementary Table 1. Details of the lipid biomarker assessment.....	2
Supplementary Table 2. Missing data of survey and blood sample variables.....	3
Supplementary Table 3. Distribution of lipid biomarkers in the study population	4
Supplementary Table 4. Median differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by tobacco use.....	5
Supplementary Table 5. Tenth and 20th percentile differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by tobacco use	6
Supplementary Table 6. Eightieth and 90th percentile differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by tobacco use	7
Supplementary Table 7. Complete case analyses of the mean differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by current tobacco use, using a stepwise exclusion of each survey year	8
Supplementary Table 8. Complete case sensitivity analyses of the mean and median differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by current cigarette smoking	9
Supplementary Table 9. Characteristics of the study participants who used snus and/or cigarettes in 1986 to 1994 by their continued use in 1999.....	10
Supplementary Figure 1. Percentage of study participants who used snus and/or cigarettes according to year of survey	11
Supplementary Figure 2. Distribution of lipid biomarkers in the study population by tobacco use	12
Supplementary Figure 3. Mean differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by current tobacco use and according to intensity of use.....	13
Supplementary Figure 4. Mean differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by current tobacco use and according to calendar period	14
Supplementary Figure 5. Age-specific discontinuation percentages of the study participants who used snus and/or cigarettes in 1986 to 1994 according to the follow-up survey in 1999	15
Supplementary Figure 6. Differences in total cholesterol, LDL cholesterol, apolipoprotein B, apolipoprotein A1, and apolipoprotein B/A1-ratio in men who used snus and/or cigarettes in 1986 to 1994 by their continued use in 1999.....	16

Supplementary Text 1 Details of the parametric model assumptions

The assumptions of the multivariable linear regression model were assessed for the primary outcomes (i.e., non-high-density lipoprotein [HDL] cholesterol, HDL cholesterol, and triglycerides). (i) The linearity assumption between outcomes and independent variables was assessed via 3-knot restricted cubic splines [Orsini N, Greenland S. A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. *Stata J.* 2011;11(1):1-29], with evidence of non-linear relationships of age and BMI (p value < 0.05; transformed accordingly). (ii) There was no indication of dependence of residuals by calendar year, as assessed by visual examination of scatterplots. (iii) The multicollinearity assumption was not violated, given that all tolerance values were greater than 0.1. (iv) Non-HDL and HDL concentrations had an approximate normal distribution, while triglyceride concentrations had a somewhat right-skewed distribution, with severe outliers (defined as three interquartile ranges either below the lowest quartile or above the highest quartile) ranging from 0.04% for non-HDL to 1.60% for triglycerides. Correspondingly, the residuals for non-HDL and HDL—but not for triglycerides—had an approximate normal distribution, as assessed by visual examination of kernel density plots. Severe outliers of the residuals ranged from 0.11% for non-HDL to 1.74% for triglycerides. However, the regression coefficients and the p values did not differ in sensitivity analyses that excluded the severe outliers (e.g., the coefficient of triglyceride concentrations for current snus use vs. never tobacco use changed from 0.09 to 0.08 mmol/L and the p value from 0.018 to 0.008). (v) There was no indication of heteroscedastic variance for the non-HDL and HDL residuals but slightly so for the triglyceride residuals, as assessed by visual examination of the residuals against the fitted values. However, the p values did not change in sensitivity analyses that estimated the standard errors using the Huber-White sandwich estimators (e.g., the p value for current snus use vs. never tobacco use with respect to triglyceride concentrations changed from 0.018 to 0.020). All in all, and especially considering the large sample size [Lumley T, et al. The importance of the normality assumption in large public health data sets. *Annu Rev Public Health.* 2002;23:151-69] and the concomitant use of non-parametric models (quantile regression), we felt comfortable to analyse the data in its original form, despite some problems related to normality and heteroscedasticity of the triglyceride variable.

Supplementary Table 1 Laboratory details of lipid biomarkers analyzed at the BiomarCaRE laboratory

Lipid biomarker	Unit	Assay method ^a	Coefficient of variation (%)	
			Intra-assay	Inter-assay
LDL cholesterol	mmol/L	Spectroscopic	0.79 to 4.40	2.89 to 5.05
HDL cholesterol	mmol/L	Spectroscopic	1.29 to 2.30	6.03 to 7.26
Triglycerides	mmol/L	Spectroscopic	0.66 to 3.58	4.03 to 16.14
Apolipoprotein A1	g/L	Immunoturbidimetric	0.67 to 2.71	2.91 to 8.53
Apolipoprotein B	g/L	Immunoturbidimetric	0.44 to 2.22	2.90 to 5.14

BiomarCaRE Biomarker for Cardiovascular Risk Assessment across Europe; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein

^a All assays were from Abbott Diagnostics (Abbott Park, IL, USA)

Supplementary Table 2 Missing data of survey and blood sample variables in the study population sampled in 1986 to 2014 (*n* = 5930)

Variable	No. with missing data (%)
Survey data	
Snus usage	90 (1.5)
Cigarette use	24 (0.4)
Educational level	84 (1.4)
Body mass index	16 (0.3)
Alcohol consumption ^a	14 (0.2)
Leisure-time physical activity ^b	95 (2.2)
Lipid-lowering drug use ^c	125 (2.4)
Diabetes mellitus	44 (0.7)
Blood sample data	
Total cholesterol	23 (0.4)
LDL cholesterol	229 (3.9)
HDL cholesterol	230 (3.9)
Triglycerides	229 (3.9)
Apolipoprotein A1	228 (3.8)
Apolipoprotein B	228 (3.8)

HDL high-density lipoprotein; *LDL* low-density lipoprotein

^a Included questions on strong beer (amount of alcohol 5.4%), wine (amount of alcohol 12 to 13%), and liquor/spirits (amount of alcohol 40%)

^b Based on data from 1990 to 2009 (*n* = 4370), since the surveys in 1986 and 2014 had a vastly different question on leisure time physical activity

^c Based on data from 1990 to 2014 (*n* = 5116), since the survey in 1986 had no question on lipid-lowering drugs

Supplementary Table 3 Mean and 5th to 95th percentile concentrations of lipid biomarkers in the study population ($n = 5930$), based on multiple imputed data sets ($n = 30$)

Lipid biomarker	Concentration							
	Mean ^a	Percentile ^b						
		5th	10th	25th	50th	75th	90th	95th
Total cholesterol (mmol/L)	5.92	4.03	4.40	5.05	5.84	6.70	7.52	8.05
Non-HDL cholesterol (mmol/L)	4.57	2.59	3.00	3.70	4.50	5.39	6.20	6.73
LDL cholesterol (mmol/L)	3.79	1.91	2.27	2.88	3.67	4.57	5.44	6.09
HDL cholesterol (mmol/L)	1.35	0.80	0.91	1.09	1.29	1.57	1.86	2.07
Triglycerides (mmol/L)	1.56	0.59	0.68	0.91	1.31	1.89	2.71	3.37
Apolipoprotein B1 (g/L)	1.10	0.61	0.71	0.87	1.07	1.30	1.53	1.66
Apolipoprotein A (g/L)	1.46	1.02	1.12	1.28	1.45	1.64	1.82	1.94

HDL high-density lipoprotein; *LDL* low-density lipoprotein

^a Estimated from a linear regression model

^b Estimated from a quantile regression model

Supplementary Table 4 Median differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by tobacco use and based on multiple imputed data sets (*n* = 30)

Median difference (95% CI) ^b	Tobacco use ^a			
	Never	Past	Current, snus	Current, cigarettes
Non-HDL cholesterol (mmol/L)				
Age-adjusted model	Ref.	0.14 (0.05, 0.24)	0.07 (-0.03, 0.18)	0.35 (0.23, 0.46)
Multivariable-adjusted model	Ref.	0.07 (-0.03, 0.16)	0.07 (-0.03, 0.17)	0.15 (0.04, 0.26)
HDL cholesterol (mmol/L)				
Age-adjusted model	Ref.	-0.02 (-0.05, 0.01)	0.02 (-0.01, 0.05)	-0.00 (-0.04, 0.03)
Multivariable-adjusted model	Ref.	-0.02 (-0.05, 0.01)	0.01 -(0.02, 0.04)	-0.02 (-0.05, 0.02)
Triglycerides (mmol/L)				
Age-adjusted model	Ref.	0.09 (0.03, 0.15)	0.10 (0.04, 0.16)	0.27 (0.20, 0.33)
Multivariable-adjusted model	Ref.	0.06 (0.01, 0.11)	0.05 (-0.01, 0.11)	0.26 (0.19, 0.34)

CI confidence interval; HDL high-density lipoprotein

^a Never = no history of snus or cigarette use; past = past history of snus or cigarette use; current, snus = current snus use; and current, cigarettes = current cigarette use (including non-daily)

^b Estimated from a quantile regression model adjusted for age (continuous using 3-knot restricted cubic splines, years), calendar year (continuous, year), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes). The lipid biomarkers were not adjusted for each other

Supplementary Table 5 Tenth and 20th percentile differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by tobacco use and based on multiple imputed data sets ($n = 30$)

Percentile difference (95% CI) ^b	Tobacco use ^a			
	Never	Past	Current, snus	Current, cigarettes
Non-HDL cholesterol (mmol/L)				
10th percentile	Ref.	0.00 (-0.10, 0.11)	-0.02 (-0.14, 0.10)	-0.01 (-0.13, 0.11)
20th percentile	Ref.	-0.01 (-0.10, 0.08)	0.02 (-0.07, 0.12)	0.11 (-0.02, 0.24)
HDL cholesterol (mmol/L)				
10th percentile	Ref.	0.02 (-0.02, 0.05)	0.02 (-0.01, 0.06)	0.00 (-0.03, 0.04)
20th percentile	Ref.	0.00 (-0.03, 0.04)	0.01 (-0.02, 0.04)	-0.02 (-0.05, 0.02)
Triglycerides (mmol/L)				
10th percentile	Ref.	0.02 (-0.01, 0.06)	0.03 (-0.01, 0.06)	0.07 (0.02, 0.11)
20th percentile	Ref.	0.03 (-0.00, 0.07)	0.04 (-0.00, 0.08)	0.13 (0.07, 0.19)

CI confidence interval; HDL high-density lipoprotein

^a Never = no history of snus or cigarette use; past = past history of snus or cigarette use; current, snus = current snus use; and current, cigarettes = current cigarette use (including non-daily)

^b Estimated from a quantile regression model adjusted for age (continuous using 3-knot restricted cubic splines, years), calendar year (continuous, year), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes). The lipid biomarkers were not adjusted for each other

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Supplementary Table 6 Eightieth and 90th percentile differences in non-HDL cholesterol, HDL cholesterol, and triglycerides by tobacco use and based on multiple imputed data sets ($n = 30$)

Percentile difference (95% CI) ^b	Tobacco use ^a			
	Never	Past	Current, snus	Current, cigarettes
Non-HDL cholesterol (mmol/L)				
80th percentile	Ref.	0.10 (-0.03, 0.22)	0.08 (-0.05, 0.20)	0.19 (0.05, 0.33)
90th percentile	Ref.	0.07 (-0.08, 0.21)	0.05 (-0.11, 0.20)	0.11 (-0.09, 0.31)
HDL cholesterol (mmol/L)				
80th percentile	Ref.	0.02 (-0.02, 0.06)	0.05 (0.01, 0.10)	0.00 (-0.04, 0.05)
90th percentile	Ref.	0.03 (-0.03, 0.09)	0.02 (-0.03, 0.08)	-0.04 (-0.10, 0.02)
Triglycerides (mmol/L)				
80th percentile	Ref.	0.04 (-0.05, 0.13)	0.08 (-0.04, 0.19)	0.30 (0.17, 0.42)
90th percentile	Ref.	-0.01 (-0.14, 0.12)	0.00 (-0.14, 0.14)	0.32 (0.08, 0.55)

CI confidence interval; HDL high-density lipoprotein

^a Never = no history of snus or cigarette use; past = past history of snus or cigarette use; current, snus = current snus use; and current, cigarettes = current cigarette use (including non-daily)

^b Estimated from a quantile regression model adjusted for age (continuous using 3-knot restricted cubic splines, years), calendar year (continuous, year), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes). The lipid biomarkers were not adjusted for each other

Supplementary Table 7 Complete case analyses of the mean differences in non-HDL cholesterol, HDL cholesterol, and triglycerides in current snus users and current cigarette smokers compared with never tobacco users, using a stepwise exclusion of each survey year

Included survey	Lipid biomarker concentration (mmol/L) ^{a, b}				Sample size difference (%) ^c		
	Non-HDL		HDL		Triglycerides		
	Snus	Cigarettes	Snus	Cigarettes	Snus	Cigarettes	
1986 to 2014	0.07	0.13	0.03	-0.01	0.09	0.27	-7.0 to -7.2
1990 to 2014	0.10	0.12	0.04	-0.01	0.10	0.28	-19.4 to -19.5
1986, 1994 to 2014	0.06	0.15	0.03	-0.00	0.07	0.26	-18.3 to -18.4
1986 to 1990, 1999 to 2014	0.07	0.11	0.04	-0.01	0.07	0.28	-22.3 to -22.4
1986 to 1994, 2004 to 2014	0.09	0.14	0.03	-0.01	0.11	0.26	-21.2 to -21.3
1986 to 1999, 2009 to 2014	0.06	0.14	0.04	-0.02	0.10	0.27	-21.5 to -21.7
1986 to 2004, 2014	0.06	0.11	0.02	-0.02	0.06	0.26	-20.4 to -20.5
1986 to 2009	0.08	0.13	0.02	-0.02	0.10	0.27	-19.1 to -19.2

HDL high-density lipoprotein

^a Bold text denotes statistically significant findings (p value < 0.05). Estimates were derived from linear regression models

^b Adjusted for age (continuous using 3-knot restricted cubic splines, years), calendar year (continuous, year), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes). The lipid biomarkers were not adjusted for each other

^c Compared with the 5930 men eligible and included in the main survey sample

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Supplementary Table 8 Complete case sensitivity analyses of the mean and median differences in non-HDL cholesterol, HDL cholesterol, and triglycerides in current cigarette smokers compared with never tobacco users

	Lipid biomarker (mmol/L) ^a					
	Non-HDL cholesterol		HDL cholesterol		Triglycerides	
	Mean	Median	Mean	Median	Mean	Median
Complete case analysis						
Survey in 1986 to 2014 ^b						
Multivariable model ^c	0.13	0.15	-0.01	-0.02	0.27	0.27
Multivariable model ^c + adjustment for lipid-lowering drug use ^d	0.14	0.15	-0.01	-0.02	0.27	0.27
Multivariable model ^c + exclusion of lipid-lowering drug users ^d	0.16	0.17	-0.01	-0.02	0.25	0.27
Survey in 1990 to 2014 ^e						
Multivariable model ^c	0.12	0.15	-0.01	-0.01	0.28	0.26
Multivariable model ^c + adjustment for lipid-lowering drug use ^f	0.14	0.16	-0.01	-0.02	0.28	0.27
Multivariable model ^c + exclusion of lipid-lowering drug users ^f	0.15	0.17	-0.01	-0.02	0.26	0.26
Survey in 1990 to 2009 ^g						
Multivariable model ^c	0.12	0.19	-0.01	-0.02	0.28	0.27
Multivariable model ^c + adjustment for physical activity ^h	0.11	0.17	-0.01	-0.02	0.27	0.24

HDL high-density lipoprotein

^a Bold text denotes statistically significant findings (p value < 0.05). Estimates were derived from linear and quantile regression models

^b n = 5504–5406, 5511–5413, and 5512–5414 for non-HDL cholesterol, HDL cholesterol, and triglycerides, respectively, in the multivariable models

^c Adjusted for age (continuous using 3-knot restricted cubic splines, years), calendar year (continuous, year), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes).

^d Further adjusted for (or restricted by) lipid-lowering drug use (no or yes [n = 398]) under the assumption that that no one in the survey in 1986 used lipid-lowering drugs

^e n = 4771–4673, 4778–4680, and 4779–4681 for non-HDL cholesterol, HDL cholesterol, and triglycerides, respectively, in the multivariable models

^f Further adjusted for (or restricted by) lipid-lowering drug use (no or yes [n = 398])

^g n = 4059–3987, 4063–3991, and 4064–3991 for non-HDL cholesterol, HDL cholesterol, and triglycerides, respectively, in the multivariable models

^h Further adjusted for physical activity (almost none, light-effort ≥ 1 h/week, or high-effort ≥ 1 h/week)

Supplementary Table 9 Characteristics of the study participants who used snus and/or cigarettes in 1986 to 1994 by their continued use in 1999

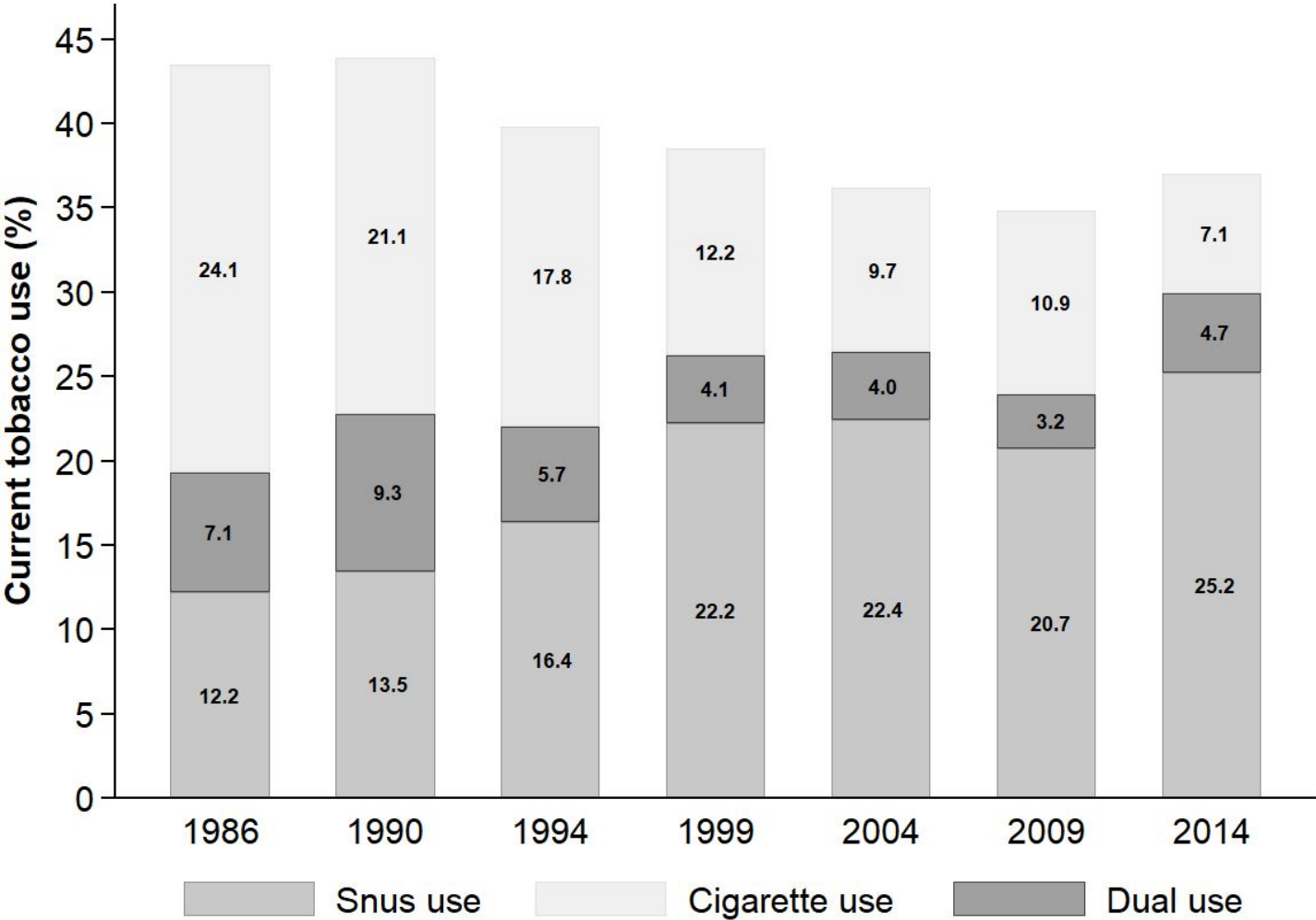
Characteristics	Snus user in 1986 to 1994 (<i>n</i> = 381)		Cigarette user in 1986 to 1994 (<i>n</i> = 455)	
	Stopped by 1999	Continued by 1999	Stopped by 1999	Continued by 1999
Participants (<i>n</i>)	80	301	203	252
Tobacco use (1999)				
Current use of snus (%)	—	100	43.0	29.2
Current use of cigarettes (%)	13.8	18.6	—	100
Covariates (1999) ^a				
Age (median, years)	55.5 (47.0–62.0)	52.0 (43.0–63.0)	56.0 (46.0–67.0)	53.0 (46.0–63.0)
University education (%)	11.8 (6.5–20.4)	7.8 (5.3–11.3)	8.9 (5.6–13.7)	11.0 (7.7–15.6)
Body mass index ≥ 30 kg/m ² (%)	23.6 (15.5–34.2)	19.9 (15.5–25.2)	20.4 (15.3–26.6)	13.1 (9.4–17.9)
Alcohol consumption at least once/week (%) ^b	36.1 (26.1–47.4)	37.3 (31.6–43.3)	44.3 (37.6–51.2)	37.9 (31.9–44.3)
High-effort physical activity ≥ 1 h/week (%)	23.7 (15.6–34.4)	27.0 (22.1–32.6)	26.1 (20.4–32.7)	16.2 (12.1–21.5)
Use of lipid-lowering drugs (%)	10.3 (5.3–19.0)	4.9 (2.8–8.5)	6.8 (4.0–11.2)	6.0 (3.5–10.1)
Diagnosis of diabetes (%)	2.4 (0.6–9.1)	7.9 (5.1–12.0)	10.2 (6.7–15.3)	2.5 (1.1–5.6)

^a All values, except age, were standardized to the age distribution (<45, 45–54, and ≥ 55 years) of the entire snus sample and smoking sample, respectively. Numbers in parentheses represent interquartile ranges (continuous variables) or 95% confidence intervals (categorical variables)

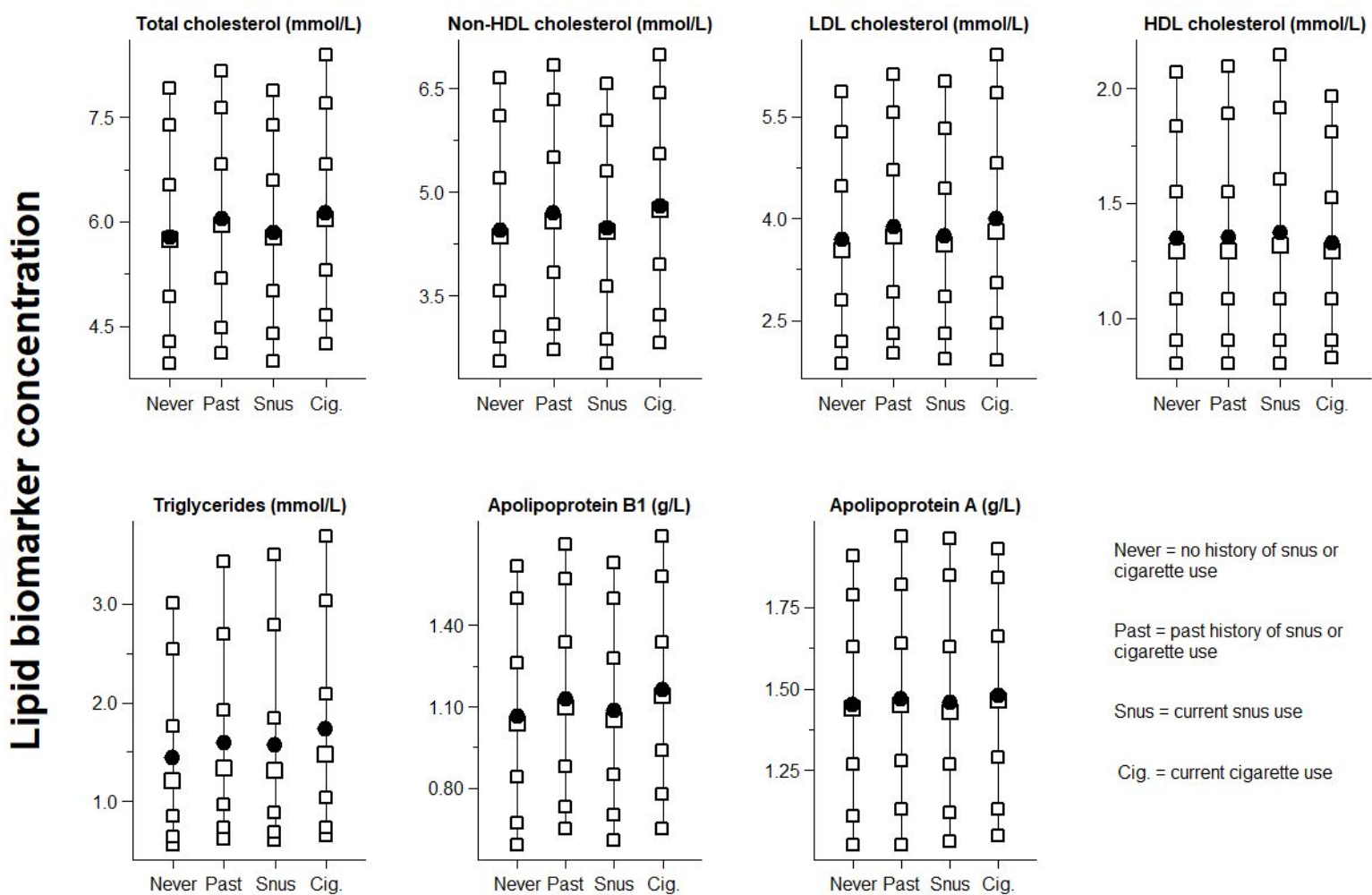
^b Included questions on strong beer (amount of alcohol 5.4%), wine (amount of alcohol 12 to 13%), and liquor/spirits (amount of alcohol 40%)

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Supplementary Figure 1 Percentage of study participants who used snus and/or cigarettes according to year of survey (1986 to 2014), based on complete data on both snus and cigarette use (*n* = 5831)



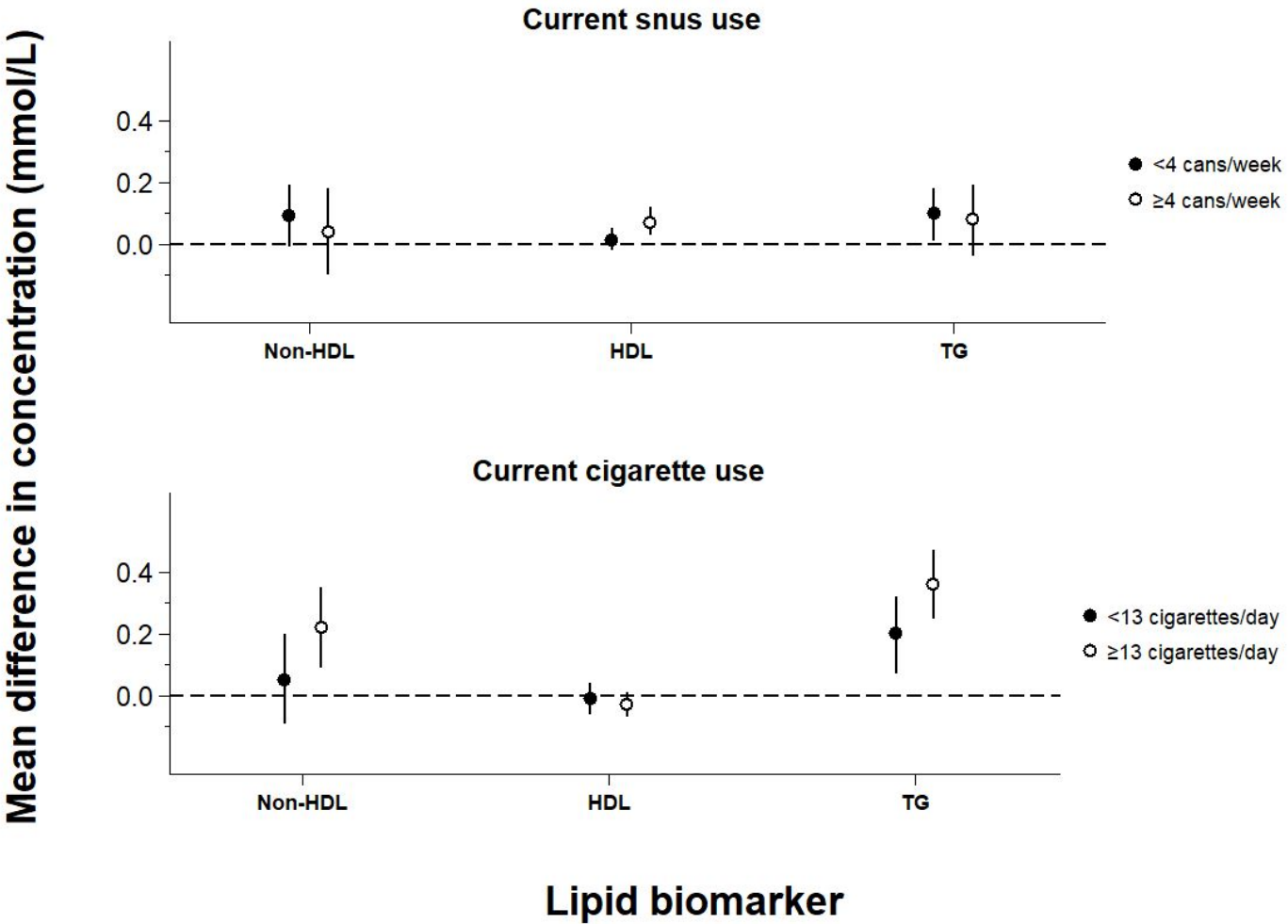
Supplementary Figure 2 Mean and 5th to 95th percentile concentrations of lipid biomarkers in the study population ($n = 5930$), by tobacco use and based on multiple imputed data sets ($n = 30$). The *solid dots* represent mean concentrations and the *hollow squares* represent percentile concentrations (5th, 10th, 25th, 50th, 75th, 90th, and 95th; ascending order on the y-axis). The symbols for the mean and 50th percentile concentrations are enlarged to improve comparability. Note that the scales of the y-axis differ between lipid biomarkers (abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein)



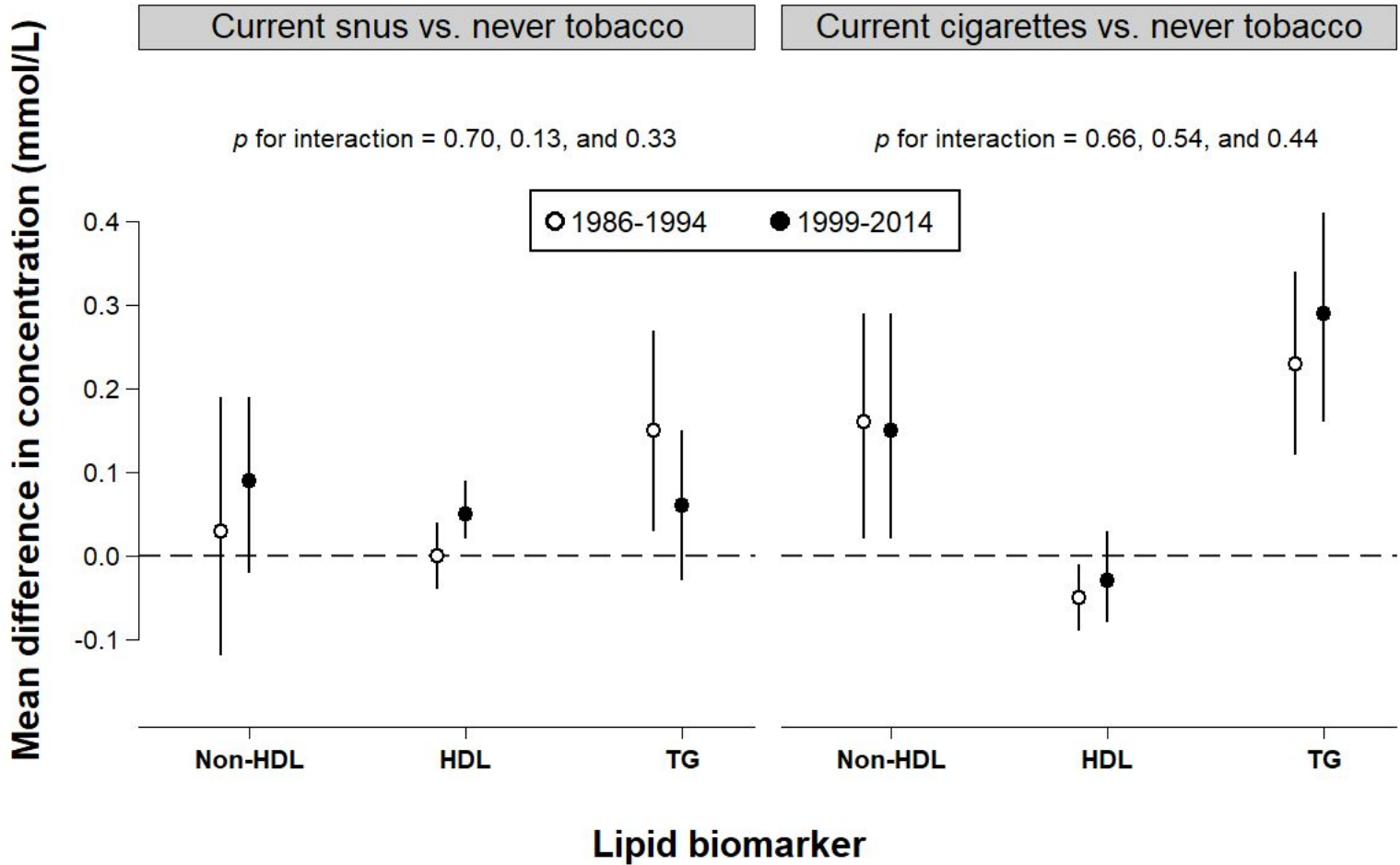
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Supplementary Figure 3 Mean differences in non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, and triglycerides (TG) by current tobacco use and according to intensity of use (compared to no history of snus or cigarette use), based on multiple imputed data sets ($n = 30$).

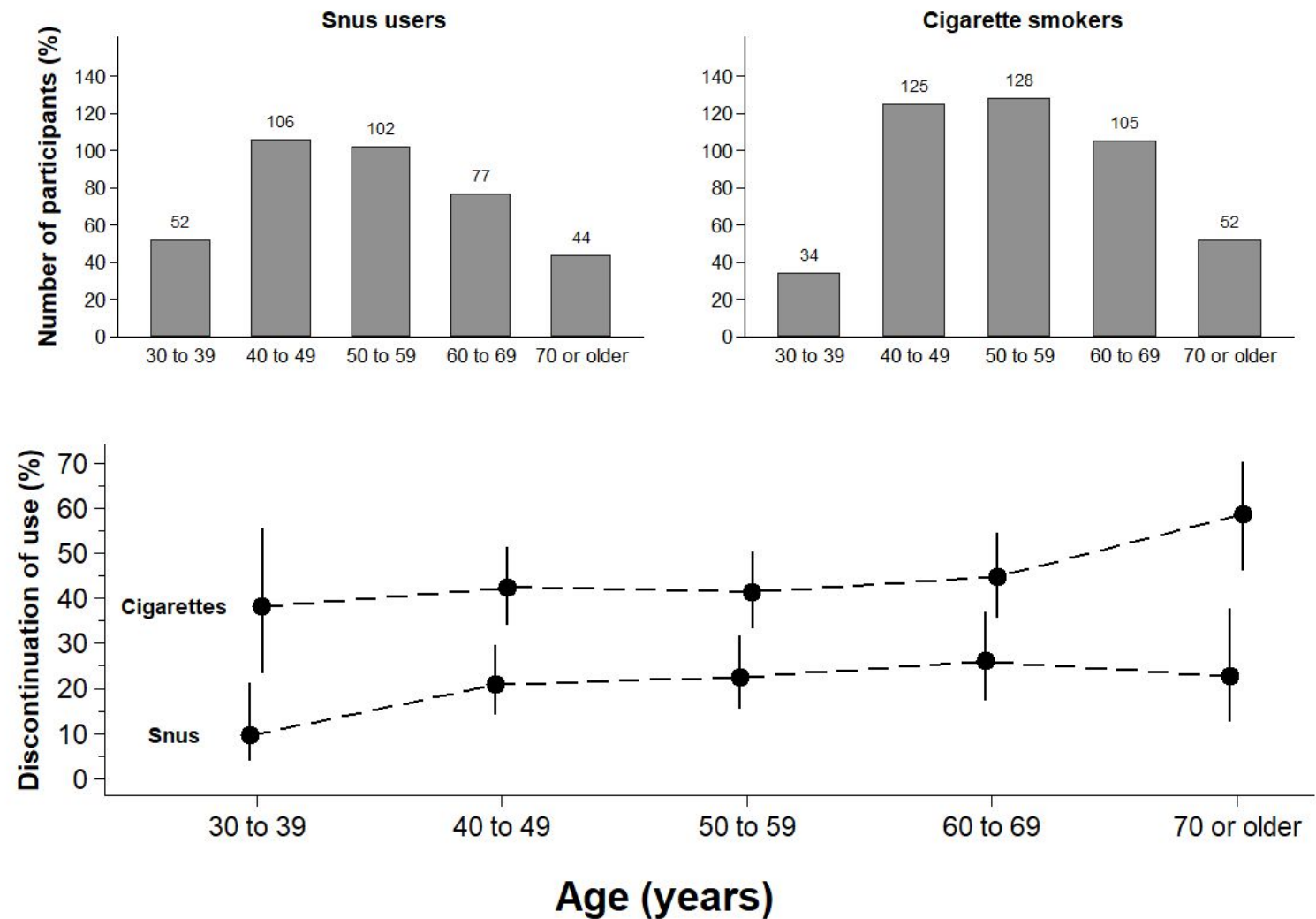
The *solid dots* and the *hollow dots* represent the estimated mean differences (*solid lines* 95% confidence intervals) for low- and high-intensity use, respectively. The estimates were derived from a linear regression model adjusted for age (continuous using 3-knot restricted cubic splines, years), calendar year (continuous, year), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes). The lipid biomarkers were not adjusted for each other. The *dashed lines* represent the cut-off for statistical significance (p value < 0.05)



Supplementary Figure 4 Mean differences in non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, and triglycerides (TG) by current tobacco use and according to calendar period (1986 to 1994, 1999 to 2014), based on multiple imputed data sets ($n = 30$). The *solid dots* and the *hollow dots* represent the estimated mean differences (*solid lines* 95% confidence intervals) for snus use and cigarette smoking, respectively. The estimates were derived from a linear regression model adjusted for age (continuous using 3-knot restricted cubic splines, years), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), and diagnosis of diabetes (no or yes). The lipid biomarkers were not adjusted for each other. The *dashed lines* represent the cut-off for statistical significance (p value < 0.05). The reported p values for interaction were calculated by including an interaction term between tobacco status and calendar period in the linear regression model and testing its coefficients equal to zero



Supplementary Figure 5 Age-specific discontinuation percentages of the study participants who used snus and/or cigarettes in 1986 to 1994 ($n = 381$ and 455 , respectively) according to the follow-up survey in 1999. In the upper panel, the *histograms* details the number of participants who used snus and/or cigarettes in 1986 to 1994 in each age category. In the lower panel, the *dots* represent the age-specific discontinuation percentage (*solid lines* 95% confidence intervals) for cigarette smoking and snus use in 1999. The *dashed lines* are added to facilitate between-age group comparisons of each tobacco habit



Supplementary Figure 6 Differences in total cholesterol (TC), low-density lipoprotein cholesterol (LDL), apolipoprotein B (ApoB), apolipoprotein A1 (ApoA), and apolipoprotein B/A1-ratio (Apo-ratio) in men who used snus and/or cigarettes in 1986 to 1994 by their continued use in 1999 (yes vs. no; based on multiple imputed data sets [$n = 30$]). The *solid dots* represent the estimated mean differences (*solid lines* 95% confidence intervals) from a linear regression model. The estimates were adjusted for age (continuous using 3-knot restricted cubic splines, years), educational level (university or non-university), body mass index (continuous using 3-knot restricted cubic splines, kg/m²), alcohol consumption (never, less than once/week, or at least once/week), diagnosis of diabetes (no or yes), lipid-lowering drug use (no or yes), and physical activity (almost none, light-effort ≥ 1 h/week, or high-effort ≥ 1 h/week). The lipid biomarkers were not adjusted for each other. The *dashed lines* represent the cut-off for statistical significance (p value < 0.05)

