

**SUPPLEMENTAL MATERIAL**

Hypothetical interventions and risk of myocardial infarction in a general population. Application of the parametric g-formula in a longitudinal cohort study: The Tromsø Study

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## Measurements

In Tromsø 2 (1979–80), blood pressure was measured by personnel trained by physicians and by listening to tape recordings of Korotkoff sounds, which were produced by the London School of Hygiene and Tropical Medicine (United Kingdom). After one-minute seated rest, two readings, separated by a 1-minute interval, were taken by using a standard stethoscope and mercury sphygmomanometer (ERKAmeter; ERKA, Bad Toltz, Germany). The mean of the readings were used in the analysis. The first and fifth Korotkoff phases represented systolic and diastolic blood pressure, respectively. In Tromsø 3 (1986–87), Tromsø 4 (1994–95), Tromsø 5 (2001) and Tromsø 6 (2007–08), blood pressure was measured with an oscillometric digital automatic device by trained personnel (by Dinamap Vital Signs Monitor; Criticon Inc, Tampa, FL, in Tromsø 3–5, and by Dinamap Procare 300 monitor, GE Healthcare, Oslo; Norway in Tromsø 6). After participants rested for 2 minutes in a sitting position, three readings were taken on the upper right arm, separated by 1-minute intervals.

Non-fasting blood samples were analyzed by standard methods at the Department of Laboratory Medicine, University Hospital of Northern Norway. In Tromsø, serum total cholesterol was measured directly by using the enzymatic oxidase method and a commercially available kit (Boehringer- Mannheim, Mannheim, Germany). In Tromsø 3–6, serum total cholesterol was analyzed within 10 h by enzymatic colorimetric methods (CHOD-PAP, Boehringer-Mannheim). Serum high-density lipoprotein cholesterol (HDL) was measured after the precipitation of low density lipoprotein with heparin and manganese chloride.

Smoking status was collected by self-report and was defined as either non-smokers or number of cigarettes smoked per day among daily smokers. In Tromsø 4, participants were asked type

specific questions about daily smoking of cigarettes/cigars/a pipe, while in Tromsø 2, 3, 5 and 6, the participants were asked about daily smoking in general. A response of “Yes” to any of these questions indicated daily smoking. Those who were categorized as daily smokers were further divided into number of cigarettes smoked per day by the question “For previous or current smokers: How many cigarettes do you, or did you smoke daily?”.

Leisure-time physical activity was defined from different questions in the surveys,<sup>1</sup> but was categorized as inactive, insufficiently active and sufficiently active in each survey. In Tromsø 2 and 3 the question on physical activity was: “Describe exercise and physical exertion in your leisure time. If your activity varies much, i.e. between summer and winter, then give an average. The question refers only to the last year. (Tick the most appropriate box): 1= Reading, watching TV, or other sedentary activity?, 2= Walking, cycling or other forms of exercise at least 4 hours a week? (include walking or cycling to work, Sunday walk/stroll, etc.), 3=Participation in recreational sports, heavy gardening etc.? (Note: duration of activity at least 4 hours a week), 4=Participation in hard training or sport competitions, regularly several times a week?”. The question has been widely used in Scandinavian studies,<sup>2</sup> and the physical activity levels have been correlated with physical fitness.<sup>3</sup> The inactive level of physical activity was defined to those who answered alternative 1; the insufficiently active level was defined to those who answered alternative 2; the sufficiently active activity level were defined to those who answered alternative 3 or 4.

In Tromsø 4 and 5, the physical activity information comprised two identical questions: one concerning light activity (not sweating or out of breath) and one concerning hard physical activity (sweating/out of breath). The question “How has your physical activity in leisure time

been during this last year? Think of your weekly average for the year. The time spent going to work counts as leisure time (hours per week)” had four alternatives: 1=none, 2=less than 1 hour, 3=1–2 hours, and 4=3 or more hours. The inactive level of physical activity was defined to those who answered alternative 1 to both questions; the sufficiently active activity level were defined to those who answered alternative 4 to the light activity question combined with alternative 3 or 4 to the hard activity question. The insufficiently active level was defined to all others.

In Tromsø 6, the physical activity information comprised three questions. Question 1 “How often do you exercise (i.e walking, skiing, swimming or training/sports)?” had five answer alternatives: 1=never, 2=less than once a week, 3=once a week, 4=2-3 times a week, 5=approximately every day. Question 2 “For how long time do you exercise? (give an average)” had four answer alternatives: 1=less than 15 minutes, 2=15-29 minutes, 3=30-60 minutes, 4=more than 1 hour. Question 3 “If you exercise - how hard do you exercise?” had three answer alternatives: 1=easy - you do not become shortwinded or sweaty, 2=you become shortwinded and sweaty, 3=hard - you become exhausted. The number of minutes per week of light or hard activity was estimated directly by combining the questions. The inactive level of activity was defined to those with no minutes of light or hard physical activity per week; Sufficiently active was defined to those with  $\geq 150$  minutes per week with light activity or  $\geq 75$  minutes per week with hard activity; Insufficiently active was defined to all others.

Work time physical activity at baseline included paid or unpaid work and was categorized in four levels: 1=mostly sedentary work (e.g. office work, mounting), 2=work that requires a lot of walking (e.g. shop assistant, light industrial work, teaching), 3=work that requires a lot of

walking and lifting (e.g. postman, nursing, construction), 4=heavy manual labor (e.g. forestry, heavy farm work, heavy construction).

Alcohol consumption was harmonized into two levels: 1=never or rarely, 2= all others. In Tromsø 2 and 3, alcohol consumption was assessed by the questions ““Are you a teetotaler?” and “If not a teetotaler, how often do you usually drink beer/ wine/ spirits”? The latter questions had five answer categories: 1=Never, or just a few times a year, 2=Once or twice a month, 3=About once a week, 4=2-3 times a week, 5=More or less daily. The never or rarely alcohol level was defined to those who answered yes to being a teetotaler or not answering higher than 1 to any of the beer/ wine/ spirits questions.

In Tromsø 4 and 5, alcohol consumption was assessed by the questions “Are you a teetotaler?” and “How many glasses of beer/wine/spirits do you normally drink in a fortnight. Put 0 if less than once a month”. The never or rarely alcohol level was defined to those who answered “yes” to being a teetotaler or not answering higher than 0 to any of the beer/ wine/ spirits questions.

In Tromsø 6, alcohol consumption was assessed by the questions “How often do you usually drink alcohol?” with 5 answer categories: 1=Never, 2=Monthly or less frequently, 3=2-4 times a month, 4=2-3 times a week, 5=4 or more times a week, and “How many units of alcohol (a beer, a glass of wine or a drink) do you usually drink when you drink alcohol?” with 5 answer categories: 1=1-2, 2=3-4, 3=5-6, 4=7-9, 5=10 or more. The never or rarely alcohol level was defined to those who answered category 1 to “How often do you usually drink alcohol?” or category 2 to “How often do you usually drink alcohol?” in combination with category 1 to

“How many units of alcohol (a beer, a glass of wine or a drink) do you usually drink when you drink alcohol?”.

#### Identification and validation of incident MI

Incident cases of MI among the participants were recorded from the date of enrollment in 1994-95 to the end of follow-up, December 31, 2013 and identified from hospital records and out-of-hospital settings, autopsy records and death certificates. The Norwegian national 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of incident and prevalent MI were identified by linkage to the discharge diagnosis registry at the University Hospital of North Norway with search for ICD 8 codes 410-414, 427, 795-796 in the period 1969-1979, ICD 9 codes 410-414, 427.5, 798 and 799 in the period 1980-98, and thereafter ICD 10 codes I20-I25, I46, R96, R98 and R99. The University Hospital is the only hospital in the area serving the Tromsø population. Modified WHO MONICA/MORGAM criteria for MI were used and included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers and autopsy reports when applicable. Linkage to the National Causes of Death Registry allowed identification of fatal incident cases of MI that occurred as out-of-hospital deaths, including deaths that occurred outside of Tromsø, as well as information on all-cause mortality. Information from the death certificates was used to collect relevant information of the event from additional sources such as autopsy reports and records from nursing homes, ambulance services and general practitioners. Dates of emigration were obtained from the Population Registry of Norway. Adjudication of hospitalized and out-of-hospital events was performed by an independent endpoint committee.

Supplemental Table 1. Covariates Used to Model Incidence of MI. The Tromsø Study 1994-2008.

Variable	Years assessed	Type of model when used as dependent variable	Functional form when used as predictor
Non-modifiable, baseline			
Age	1994-95	Not predicted	Linear and quadratic term
Sex	1994-95	Not predicted	Binary
Education	1994-95	Not predicted	4 categories <sup>a</sup>
Marital status	1994-95	Not predicted	5 categories <sup>b</sup>
Physical activity at work	1994-95	Not predicted	4 categories <sup>c</sup>
Non modifiable, pre-baseline			
Smoking history	1979-80 or 86-87	Not predicted	6 categories <sup>d</sup>
Total cholesterol	1979-80 or 86-87	Not predicted	Linear
Systolic blood pressure	1979-80 or 86-87	Not predicted	Linear
Body mass index	1979-80 or 86-87	Not predicted	Linear on log scale
HDL cholesterol	1979-80 or 86-87	Not predicted	Linear
Physical activity	1979-80 or 86-87	Not predicted	3 categories <sup>e</sup>
Alcohol intake	1979-80 or 86-87	Not predicted	Binary <sup>f</sup>
Directly modifiable			
Smoking	All periods	Logistic, log-linear	4 categories <sup>g</sup>
Physical activity	All periods	Nested logistic	3 categories <sup>e</sup>
Alcohol intake	All periods	Logistic	Binary <sup>f</sup>
Indirectly modifiable			
Body mass index	All periods	Linear on log scale	6 categories <sup>h</sup>
Diabetes	All periods	Logistic to failure	Binary
Systolic blood pressure	All periods	Linear	6 categories <sup>i</sup>
Total cholesterol	All periods	Linear	6 categories <sup>j</sup>
High density lipoprotein	All periods	Linear	6 categories <sup>k</sup>

<sup>a</sup>Education; ≤ 10 years of schooling, High school diploma, College or university < 4 years, College or university ≥ 4 years.

<sup>b</sup>Marital status; Single, married/partnership, widow/widower, divorced, separated.

<sup>c</sup>Physical activity at work; mostly sedentary work (e.g. office work, mounting), work that requires a lot of walking (e.g. shop assistant, light industrial work, teaching), work that requires a lot of walking and lifting (e.g. postman, nursing, construction), heavy manual labor (e.g. forestry, heavy farmwork, heavy construction).

<sup>d</sup>Smoking history; never smoker, previous smoker, cigarettes per day 1-4, 5-14, 15-24, ≥25.

<sup>e</sup>Leisure time physical activity; inactive= no minutes of light or hard physical activity per week, sufficiently active = ≥150 minutes per week with light activity or ≥75 minutes per week with hard activity, insufficiently active = all others.

<sup>f</sup>Alcohol intake; never or less than one unit per month, one or more units per month.

<sup>g</sup>Smoking, cigarettes per day 0,1-4, 5-14, ≥15.

<sup>h</sup>Body mass index, kg/m<sup>2</sup>; <20, 20-23.99, 24-25.99, 26-27.99, 28-29.99, ≥30.

<sup>i</sup>Systolic blood pressure, mmHg; <115, 115-124, 125-134, 135-144, 145-154, ≥155.

<sup>j</sup>Total cholesterol, mmol/l; <4.91, 4.91-5.42, 5.43-5.94, 5.95-6.45, 6.46-7.75, ≥7.76

<sup>k</sup>High density lipoprotein cholesterol, mmol/l; <1, 1-1.19, 1.20-1.39, 1.40-1.59, 1.60-1.89, ≥1.90

Supplemental Table 2. Hazard ratios for MI<sup>a</sup>. The Tromsø Study 1994-2008.

Characteristic	HR (95 % CI)
Daily smoking, cigarettes per day	
0	1 (Reference)
1-4	1.58 (1.02, 2.45)
5-14	2.12 (1.82, 2.47)
≥14	2.39 (2.01, 2.84)
Physical activity <sup>b</sup>	
Inactive	1 (Reference)
Insufficiently active	0.92 (0.74, 1.14)
Sufficiently active	0.87 (0.70, 1.08)
Moderate drinkers of alcohol <sup>c</sup> , yes/no	0.79 (0.69, 0.90)
Body Mass Index, kg/m <sup>2</sup>	1.13 (1.06, 1.21)
Systolic Blood pressure, mmHg	1.34 (1.27, 1.43)
Total cholesterol, mmol/L	1.41 (1.33, 1.50)

MI, myocardial infarction; HR, hazard ratio; CI confidence interval

<sup>a</sup>Cox proportional hazard regression models with updated values of risk factors during follow-up. HRs are adjusted for all listed variables and for age, sex, education, high-density lipoprotein cholesterol, diabetes mellitus, marital status, and work time physical activity. HRs for the continuous variables are presented per standard deviation.

<sup>b</sup>Leisure time physical activity; inactive= no minutes of light or hard physical activity per week, sufficiently active = ≥150 minutes per week with light activity or ≥75 minutes per week with hard activity, insufficiently active = all others.

<sup>c</sup>Alcohol intake; never or less than one unit per month, one or more units per month.



Supplemental Table 3 Descriptive Characteristics Under Feasible and Intensive Interventions by Survey<sup>a</sup>. The Tromsø Study 1994-2008.

	Tromsø 4 1994-95	Tromsø 5 2001	Tromsø 6 2007-08
Feasible hypothetical interventions <sup>b</sup>			
Body mass index, kg/m <sup>2</sup>	24.2 ( 2.6)	25.2 ( 3.0)	25.4 ( 2.9)
Systolic blood pressure, mmHg	129 (10.9)	131 (11.2)	131 (12.1)
Total cholesterol, mmol/L	5.7 ( 0.7)	5.8 ( 0.6)	5.5 ( 0.7)
Daily smoking, %			
Non-smoker	29.4 (4383)	30.3 (1416)	31.6 (2129)
Previous smoker	39.9 (5947)	47.2 (2207)	53.5 (3609)
Daily smoker	30.8 (4588)	22.6 (1056)	14.9 (1006)
Leisure time physical activity <sup>d</sup> , %			
Inactive	5.8 ( 869)	4.0 ( 179)	3.9 ( 261)
Insufficiently active	32.4 (4851)	30.1 (1363)	43.0 (2890)
Sufficiently active	61.8 (9235)	65.9 (2982)	53.1 (3570)
Alcohol intake <sup>e</sup> , % never or rarely	23.8 (3534)	20.2 ( 824)	26.3 (1771)
Intensive hypothetical interventions <sup>c</sup>			
Body mass index, kg/m <sup>2</sup>	23.7 ( 1.8)	24.2 ( 1.5)	24.3 ( 1.4)
Systolic blood pressure, mmHg	118 ( 4.0)	118 ( 4.2)	118 ( 5.0)
Total cholesterol, mmol/L	5.0 ( 0.3)	5.1 ( 0.3)	5.0 ( 0.4)
Daily smoking, %			
Non-smoker	29.4 ( 4383)	30.3 ( 1416)	31.6 ( 2129)
Previous smoker	70.6 (10535)	69.7 ( 3263)	68.4 ( 4615)
Daily smoker	0	0	0
Leisure time physical activity <sup>d</sup> , %			
Inactive	0	0	0
Insufficiently active	0	0	0
Sufficiently active	100%	100%	100%
Alcohol intake <sup>e</sup> , % never or rarely	0	0	0

<sup>a</sup>Values are mean (standard deviation) or percent (number).

<sup>b</sup>The 6 feasible interventions were defined as follows (1) 20% of daily smokers quit smoking, (2) 20% move to sufficient physical activity, (3) 20% of non-drinkers become moderate drinkers of alcohol, (4) Lower BMI to 25 kg/m<sup>2</sup> or lose 10% BMI if BMI ≥ 27.78 kg/m<sup>2</sup>, (5) Lower total cholesterol to 6.22 mmol/L (240 mg/dL), (6) Lower systolic blood pressure to 140 mmHg.

<sup>c</sup>The 6 intensive interventions were defined as follows: (1) All daily smokers quit smoking, (2) All move to sufficient physical activity, (3) All non-drinkers become moderate drinkers of alcohol, (4) Lower BMI to 25 kg/m<sup>2</sup>, (5) Lower total cholesterol to 5.18 mmol/L (200 mg/dL), (6) Lower systolic blood pressure to 120 mmHg.

<sup>d</sup>Inactive = No minutes of light or hard physical activity per week, Sufficiently active = ≥150 minutes per week with light activity or ≥75 minutes per week with hard activity

<sup>e</sup>Alcohol intake = never or less than one unit per month

Supplemental Table 4. Risk of MI Under Feasible and Intensive Hypothetical Interventions Using Multiple Imputations on Missing Values at Pre-baseline or at Baseline<sup>a</sup>. The Tromsø Study 1994–2008.

	19-year risk of MI, %	Population risk ratio	Population risk difference <sup>b</sup>
Natural course, no intervention	7.70	1	0
Feasible hypothetical interventions			
Lifestyle change <sup>c</sup>	6.65	0.90	-0.71
Lifestyle change and risk factor control <sup>d</sup>	5.13	0.70	-2.22
Intensive hypothetical interventions			
Lifestyle change <sup>e</sup>	5.60	0.76	-1.75
Lifestyle change and risk factor control <sup>f</sup>	2.27	0.31	-5.09

BMI, body mass index; SBP, systolic blood pressure; TC, total serum cholesterol

<sup>a</sup>Estimated using the parametric g-formula with fixed covariates: age, education, former smoking, marital status, and work time physical activity; and time-varying covariates: smoking, physical activity, alcohol use, body mass index, SBP, total cholesterol, high-density lipoprotein cholesterol, and diabetes mellitus.

<sup>b</sup>Observed risk, 7.70%.

<sup>c</sup>20% of smokers quit smoking, 20% move to sufficient leisure-time physical activity defined as  $\geq 150$  minutes per week with light activity or  $\geq 75$  minutes per week with hard activity, 20% of non-drinkers become moderate drinkers of alcohol, lower BMI to  $< 25$  kg/m<sup>2</sup> or lose 10% BMI if BMI  $\geq 27.78$  kg/m<sup>2</sup>.

<sup>d</sup>Lifestyle change + lower TC to  $< 5.18$  mmol/l (200mg/dL), lower SBP to  $< 120$  mmHg.

<sup>e</sup>All smokers quit smoking, all perform sufficient leisure-time physical activity defined as  $\geq 150$  minutes per week with light activity or  $\geq 75$  minutes per week with hard activity, all become moderate drinkers of alcohol, lower BMI to  $< 25$  kg/m<sup>2</sup>.

<sup>f</sup>Lifestyle change + lower TC to  $< 5.18$  mmol/l (200mg/dL), lower SBP to  $< 120$  mmHg.

Supplemental Table 5. Estimated 19-years MI Risk Under Feasible<sup>a</sup> Joint Hypothetical Intervention on Lifestyle and Metabolic Risk Factors Compared to Natural Scenario, Under Various Modeling Orders of Time-varying Covariates. The Tromsø Study 1994-2008.

Order of time-varying covariates <sup>b</sup>	19-Year risk of MI, natural scenario (%) (95% CI)	19-Year risk of MI, joint intervention (%) (95% CI)	Population Risk ratio (95% CI)	Population Risk difference (95% CI)
A	7.48 (6.78, 7.82) <sup>c</sup>	5.21 (4.38, 6.05)	0.70 (0.61, 0.81)	-2.26 (-2.88, -1.45)
B	7.48 (6.78, 7.82) <sup>c</sup>	5.21 (4.38, 6.06)	0.70 (0.61, 0.80)	-2.27 (-2.88, -1.46)
C	7.45 (6.78, 7.88) <sup>c</sup>	5.22 (4.40, 6.06)	0.70 (0.61, 0.80)	-2.23 (-2.85, -1.46)
D	7.44 (6.79, 7.82) <sup>c</sup>	5.20 (4.38, 6.03)	0.70 (0.61, 0.80)	-2.23 (-2.90, -1.46)
E	7.44 (6.78, 7.83) <sup>c</sup>	5.23 (4.39, 6.04)	0.70 (0.61, 0.80)	-2.20 (-2.85, -1.44)
F	7.43 (6.76, 7.82) <sup>c</sup>	5.22 (4.38, 6.04)	0.70 (0.61, 0.80)	-2.21 (-2.88, -1.45)
G	7.45 (6.77, 7.84) <sup>c</sup>	5.21 (4.39, 6.03)	0.70 (0.61, 0.81)	-2.24 (-2.86, -1.45)
H	7.43 (6.76, 7.85) <sup>c</sup>	5.21 (4.39, 6.04)	0.70 (0.61, 0.81)	-2.22 (-2.87, -1.44)
I	7.42 (6.78, 7.84) <sup>c</sup>	5.22 (4.39, 6.03)	0.70 (0.61, 0.81)	-2.20 (-2.87, -1.45)
J	7.43 (6.78, 7.84) <sup>c</sup>	5.20 (4.38, 6.05)	0.70 (0.61, 0.81)	-2.22 (-2.86, -1.43)
K	7.43 (6.79, 7.83) <sup>c</sup>	5.20 (4.38, 6.03)	0.70 (0.61, 0.80)	-2.23 (-2.86, -1.45)
L <sup>d</sup>	7.24 (6.67, 7.72) <sup>e</sup>	5.06 (4.25, 5.80)	0.70 (0.60, 0.80)	-2.19 (-2.83, -1.42)

CI, Confidence interval; MI, Myocardial infarction; PRR, Population Risk Ratio; PRD, Population risk difference

<sup>a</sup>20% of smokers quit smoking, 20% move to sufficient physical activity defined as  $\geq 150$  minutes per week with light activity or  $\geq 75$  minutes per week with hard activity, 20% of non-drinkers become moderate drinkers of alcohol, lower BMI to 25 kg/m<sup>2</sup> or lose 10% BMI if BMI  $\geq 27.78$  kg/m<sup>2</sup>, lower TC to  $< 6.22$  mmol/l (240mg/dL), lower SBP to  $< 140$  mmHg.

<sup>b</sup>Order of time-varying covariates:

A: Smoking, physical activity, alcohol use, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

B: Smoking, alcohol use, physical activity, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

C: Smoking, alcohol use, body mass index, physical activity, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

D: Smoking, body mass index, physical activity, alcohol use, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

E: Physical activity, smoking, alcohol use, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

F: Physical activity, smoking, body mass index, alcohol use, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

G: Alcohol use, smoking, physical activity, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

H: Smoking, physical activity, alcohol use, body mass index, systolic blood pressure, diabetes, total serum cholesterol, high-density lipoprotein.

I: Smoking, physical activity, alcohol use, body mass index, systolic blood pressure, total serum cholesterol, diabetes, high-density lipoprotein.

J: Smoking, alcohol use, physical activity, body mass index, total serum cholesterol, high-density lipoprotein, diabetes, systolic blood pressure.

K: Smoking, physical activity, alcohol use, body mass index, high-density lipoprotein, total serum cholesterol, systolic blood pressure, diabetes.

L: Smoking, physical activity, alcohol use, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

<sup>c</sup>Observed risk 7.64%.

<sup>d</sup>Sensitivity analysis where attendees with diabetes at baseline (Tromsø 4, 1994-95) were excluded, n=167.

<sup>e</sup>Observed risk 7.44%.

Supplemental Table 6. Estimated 19-years MI risk under intensive<sup>a</sup> joint hypothetical intervention on lifestyle and metabolic risk factors compared to natural scenario, under various modeling orders of time-varying covariates. The Tromsø Study 1994-2008.

Order of time-varying covariates <sup>b</sup>	19-Year risk of MI, natural scenario (%) (95% CI)	19-Year risk of MI, joint intervention (%) (95% CI)	Population Risk ratio (95% CI)	Population Risk difference (95% CI)
A	7.48 (6.78, 7.82) <sup>c</sup>	2.23 (1.58, 2.86)	0.30 (0.22, 0.40)	-5.24 (-5.89, -4.24)
B	7.48 (6.78, 7.82) <sup>c</sup>	2.24 (1.57, 2.86)	0.30 (0.22, 0.40)	-5.24 (-5.89, -4.24)
C	7.45 (6.78, 7.88) <sup>c</sup>	2.24 (1.57, 2.86)	0.30 (0.22, 0.40)	-5.21 (-5.87, -4.25)
D	7.44 (6.79, 7.82) <sup>c</sup>	2.24 (1.57, 2.86)	0.30 (0.22, 0.40)	-5.20 (-5.89, -4.27)
E	7.44 (6.78, 7.83) <sup>c</sup>	2.23 (1.57, 2.86)	0.30 (0.22, 0.40)	-5.20 (-5.87, -4.27)
F	7.43 (6.76, 7.82) <sup>c</sup>	2.24 (1.58, 2.86)	0.30 (0.22, 0.40)	-5.19 (-5.87, -4.25)
G	7.45 (6.77, 7.84) <sup>c</sup>	2.24 (1.58, 2.86)	0.30 (0.22, 0.40)	-5.21 (-5.88, -4.26)
H	7.43 (6.76, 7.85) <sup>c</sup>	2.24 (1.57, 2.86)	0.30 (0.22, 0.40)	-5.19 (-5.86, -4.26)
I	7.42 (6.78, 7.84) <sup>c</sup>	2.24 (1.57, 2.86)	0.30 (0.22, 0.40)	-5.18 (-5.87, -4.26)
J	7.43 (6.78, 7.84) <sup>c</sup>	2.24 (1.58, 2.86)	0.30 (0.22, 0.40)	-5.19 (-5.86, -4.25)
K	7.43 (6.79, 7.83) <sup>c</sup>	2.25 (1.58, 2.87)	0.30 (0.22, 0.40)	-5.18 (-5.86, -4.24)
L <sup>d</sup>	7.24 (6.67, 7.72) <sup>e</sup>	2.19 (1.52, 2.81)	0.30 (0.21, 0.40)	-5.06 (-5.71, -4.19)

CI, Confidence interval; MI, Myocardial infarction

<sup>a</sup>All smokers quit smoking, all perform sufficient leisure-time physical activity defined as  $\geq 150$  minutes per week with light activity or  $\geq 75$  minutes per week with hard activity, all become moderate drinkers of alcohol, lower BMI to  $< 25$  kg/m<sup>2</sup>, lower TC to  $< 5.18$  mmol/l (200mg/dL), lower SBP to  $< 120$  mmHg

<sup>b</sup>Order of time-varying covariates:

A: Smoking, physical activity, alcohol use, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

B: Smoking, alcohol use, physical activity, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

C: Smoking, alcohol use, body mass index, physical activity, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

D: Smoking, body mass index, physical activity, alcohol use, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

E: Physical activity, smoking, alcohol use, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

F: Physical activity, smoking, body mass index, alcohol use, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

G: Alcohol use, smoking, physical activity, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

H: Smoking, physical activity, alcohol use, body mass index, systolic blood pressure, diabetes, total serum cholesterol, high-density lipoprotein.

I: Smoking, physical activity, alcohol use, body mass index, systolic blood pressure, total serum cholesterol, diabetes, high-density lipoprotein.

J: Smoking, alcohol use, physical activity, body mass index, total serum cholesterol, high-density lipoprotein, diabetes, systolic blood pressure.

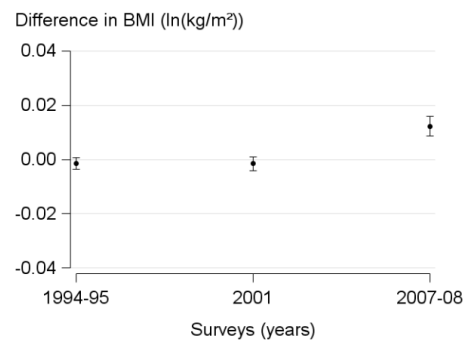
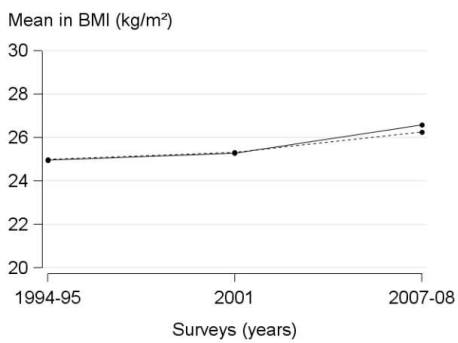
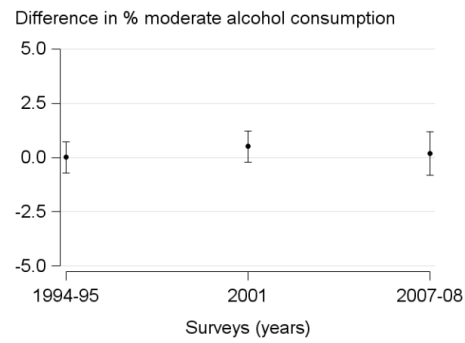
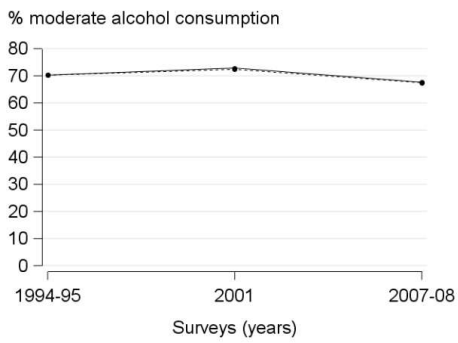
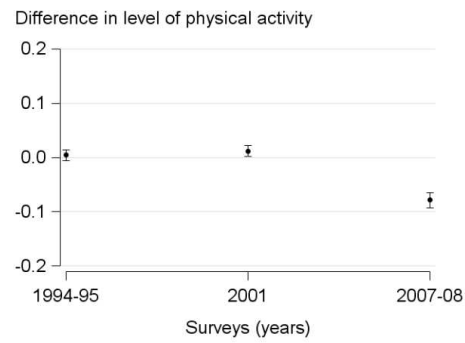
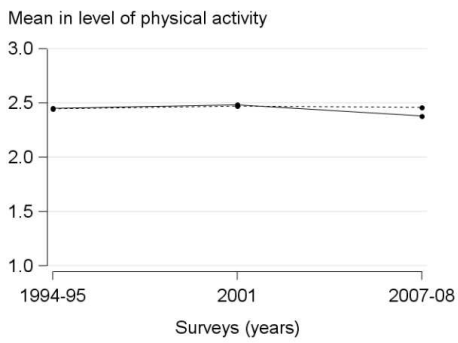
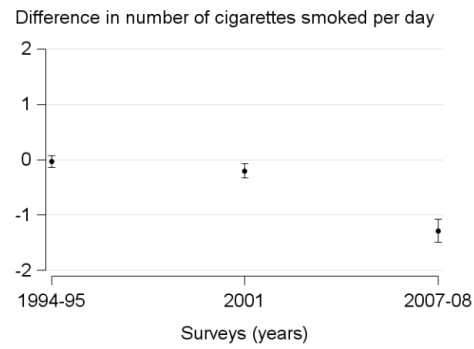
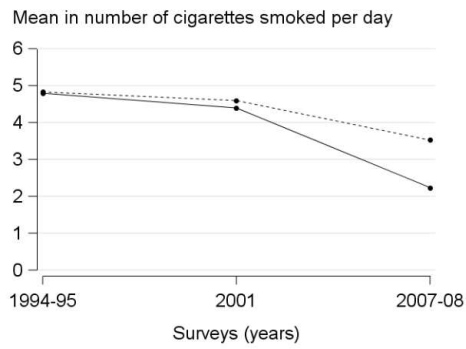
K: Smoking, physical activity, alcohol use, body mass index, high-density lipoprotein, total serum cholesterol, systolic blood pressure, diabetes.

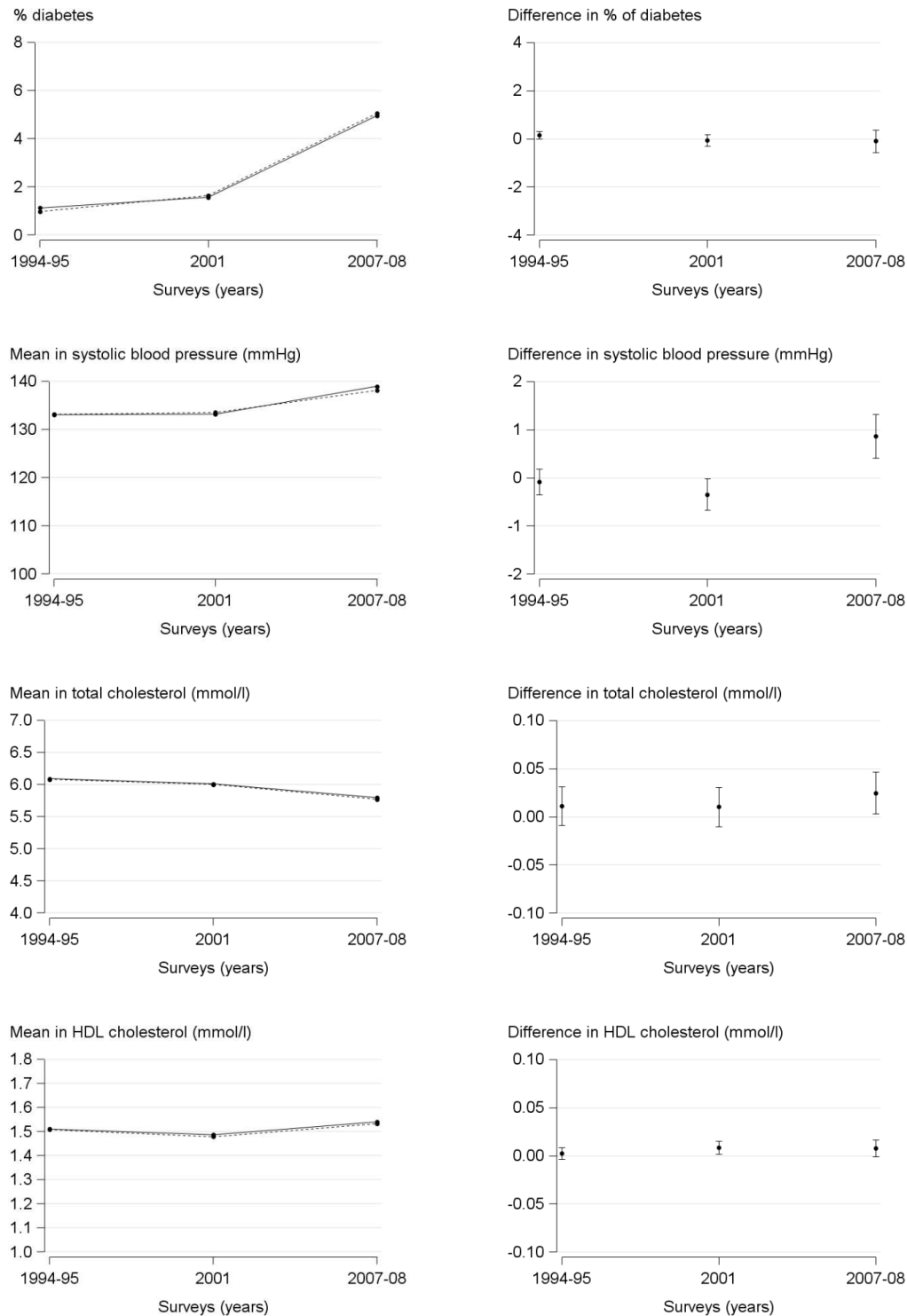
L: Smoking, physical activity, alcohol use, body mass index, diabetes, systolic blood pressure, total serum cholesterol, high-density lipoprotein.

<sup>c</sup>Observed risk 7.64%.

<sup>d</sup>Sensitivity analysis where attendees with diabetes at baseline (Tromsø 4, 1994-95) were excluded, n=167.

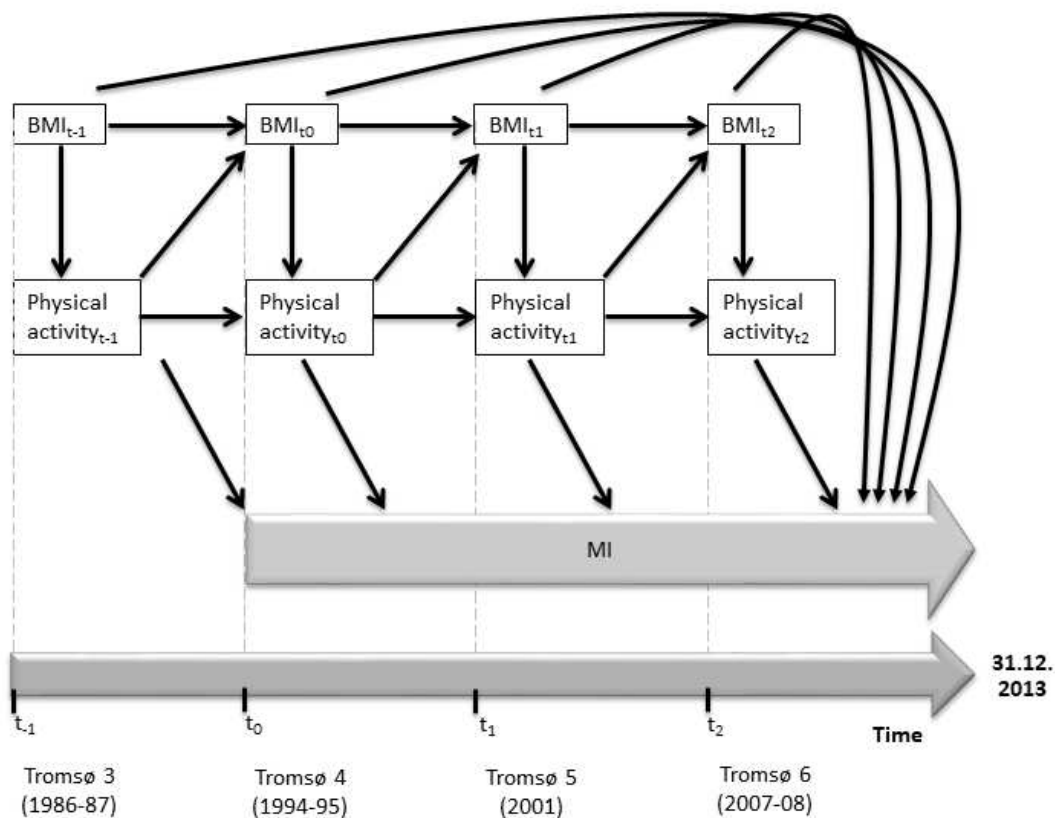
<sup>e</sup>Observed risk 7.44%.





Supplemental Figure 1. Observed and simulated means or prevalence (left column) and differences in means or prevalence with 95% confidence limits (right column) by survey. The Tromsø Study 1994-2008.

Solid lines, observed means; Dotted lines simulated means.



Supplemental Figure 2. Directed acyclic graph (DAG) showing time-dependent confounding with confounder (BMI) affected by prior exposure (physical activity). The Tromsø Study 1994-2008

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