eAppendix 1 - Methods

The Norwegian Prescription Database

From January 2004, all Norwegian pharmacies are legally required to send electronic data to this database on all prescription drugs dispensed. The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[1] Among the data collected are the patient's unique identification number (encrypted), sex, and age, as well as the date of dispensing, the drug's ATC-code, and code of reimbursement if relevant.

Health surveys conducted by the Norwegian government

From 1985 through 1999 all women and men who were 40-42 years in the start year of the survey in each county were invited. In addition persons aged 43-44 years were invited in a few counties. As the screening extended over two calendar years in some counties, the participants were 40-45 years at time of screening. All counties were included except for the capital Oslo. The surveys were partly done by means of questionnaires (e.g. for coffee consumption, smoking, exercising habits, and history of asthma, heart infarction, angina pectoris, stroke and diabetes), partly by physical measurements (e.g. for height, weight, blood pressure, triglycerides). The questionnaires were filled out in advance and delivered at the screening. In total, 395,228 individuals attended the screenings. Of these, 33,183 were excluded for various reasons (eFigure), and 362,045 were included in the analysis.

Three different questionnaires were used in the surveys, one for 1985-1994, one for 1994-1997, and one for 1997-1999. The questions about coffee consumption were changed after the first period. From 1985 to 1994, the subjects were asked how many cups of coffee they drank in total (<1, 1-4, 5-8, or 9+ cups per day), and in addition whether they drank the following types of coffee daily: boiled, filtered, instant, and decaffeinated. From 1994 to1999 the subjects were asked how many cups of boiled coffee they drank per day (continuous variable) and how many cups of other types of coffee. These data were grouped into the four categories used in 1985 to 1994 by adding up the consumption of boiled and other types of coffee. A Norwegian cup of coffee corresponds to approximately 0.15 l.

"Other types of coffee" mainly means filtered coffee. Of those screened before 1995 who reported a daily consumption of other types of coffee than boiled, 90%, 15%, and 2% reported a daily consumption of filtered, instant, and decaffeinated coffee, respectively.

The subjects were asked whether they smoked or had smoked daily, and, if yes, how many cigarettes per day. We categorized the subjects into 7 groups: never smokers, previous smokers (1-9, 10-19, and 20+ cigarettes per day), and current smokers (1-9, 10-19, and 20+ cigarettes per day).

Physical activity in leisure time was addressed in two different ways in the questionnaires. We simplified by creating a new variable with three levels (low, moderate, and high) according to the scheme shown in eTable 1.

The question on alcohol consumption (only included in the survey from 1994-1999), was: "How many times each month do you usually drink alcohol?" In addition there was a question on teetotalism (yes/no).

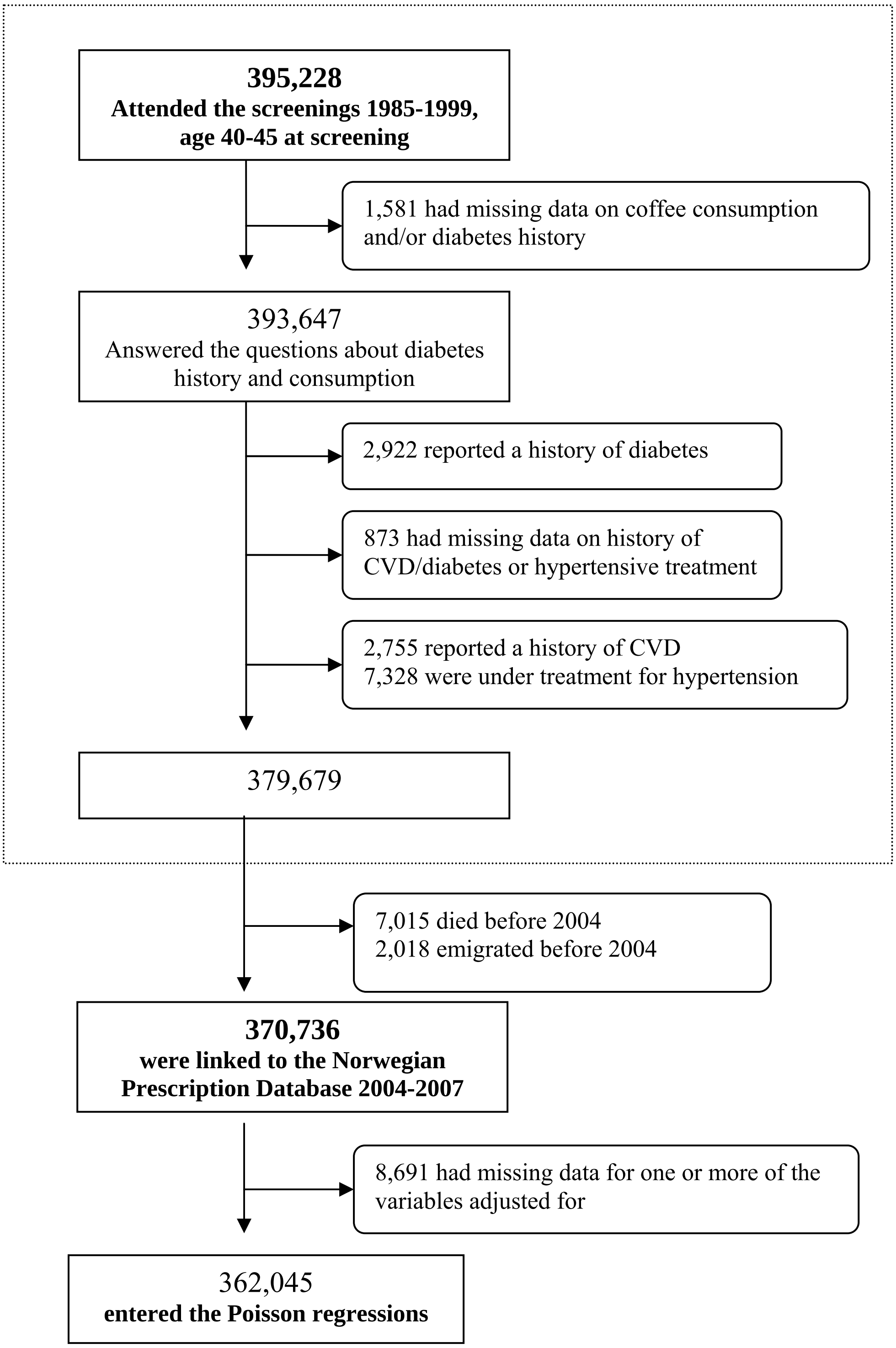
Detailed data on education were available from census data**,** which were linked to the health survey data. We trichotomized educational level into low (elementary school or less; 9 years) medium (college/high school; 10-12 years) and high (university; 13+ years).

BMI, diastolic blood pressure, and triglycerides (log-transformed) were entered as continuous variables in the main analyses. BMI was calculated as weight (kg) divided by height (m) squared, where weight was measured to the nearest ½ kg, and height to the nearest cm.

eTable 1. Physical activity. A new variable with three levels (low, medium, high) was derived from the variables used in the health surveys.[a,b] The numbers of subjects in each category group are given in parentheses.

New variable, 1985-99	Original variable, 1985-94 [a]	Original variable, 1994-99 [b]
low (n = 59,823)	sedentary (n = 45,438)	0 h/w 'serious' and <1 h/w 'light' (n = 14,385)
high (n = 63,559)	intermediate or intensive (n = 47,460)	3+ h/w 'hard' (n = 16,099)
moderate (n = 238,663)	moderate (n = 149,416)	the remaining (n = 89,247)

[a] During 1985-94, four alternatives were given (sedentary, moderate (light activity ≥4 hours/week (h/w)), intermediate (exercising ≥ 4 h/w), intensive (hard exercising / competing).
[b] During 1994-99 the subjects were asked about time spent on 'serious' (causing sweating or breathlessness) and 'light' physical activity with alternatives 0, <1, 1-2, 3+ h/w.



eFigure. Flow chart of the study population.

eAppendix 2 - Discussion

The use of drug prescriptions as an indicator of incident diabetes

The use of dispensed drugs as a proxy for type 2 diabetes eliminates the problem of incorrect self-reports caused by recall bias or other causes (see "*The use of self-reports for identifying diabetes at baseline"* below), but can also lead to false negatives (undetected cases of diabetes) and false positives (people without diabetes that are recorded as having diabetes).

False negatives: Many people with type 2 diabetes control their disease with diet, physical activity and weight loss only. According to the Norwegian Diabetes Association, about 70% of type 2 diabetes patients need medication. Further, some patients with type 2 diabetes use insulin alone to treat their disease. This means that the number of cases in our study population is an underestimate of the exact number of incident type 2 diabetes patients, and we have to make the reasonable assumption that the degree of underestimation does not depend on coffee consumption. As regards insulin users, 900 (0.26%) of the individuals in the study population who were not dispensed oral antidiabetics were dispensed insulin, but it is not possible to identify these as type 1 or type 2 patients. They were, however, evenly distributed on coffee groups (0.26%, 0.26%, 0.23%, and 0.28%, respectively, in the four groups).

False positives: Very few – if any – individuals in this age group are prescribed oral antidiabetic drugs that are reimbursed for diabetes without actually having type 2 diabetes.

The use of self-reports for identifying diabetes at baseline

The study population may have included some individuals that did not report a history of diabetes at screening even though they had a diabetes diagnoses. In Okura et al 99 (66%) out of 150 U.S. patients who actually had a diabetes diagnosis in their medical record answered "yes" when asked whether a medical provider had told them that they had diabetes.[2] In the age group 45-65 years the percentage was 77%. Margolis et al reported roughly the same sensitivity in a population of 161,808 U.S. women aged 50-79 years.[3] It should be noted, though, that 37 out of the 51 false-negative responders in Okura et al answered "yes" when asked whether they had a diagnoses of borderline diabetes.

Also, we may have included in the study population patients with undiagnosed diabetes at baseline, but in Margolis et al[3] only 3% of those not reporting diabetes had a fasting plasma glucose > 126 mg dl^{-1}. Finally, the change in the diagnostic value of the fasting plasma glucose from 140 mg dl^{-1} to 126 mg dl^{-1} between screening and 1 January 2004[4] implies that some of the individuals that would not have been diagnosed with type 2 diabetes when screened, would have been so after 1 January 2004, even though their fasting plasma glucose had not changed. However, if the proportion of individuals who for any reason incorrectly were included in (or excluded from) the study population was the same in the different coffee groups this should not affect our results.

Confounders

Poor physical shape is an important risk-factor for type 2 diabetes, and in our study population a sedentary life style was associated with incident diabetes and high coffee consumption. Adjusting for physical activity did strengthen the coffee-diabetes association, but as our measure for physical activity was coarse, a better measure would probably have strengthened the association even more.

Alcohol consumption was available only for 33% of the study population (those screened after 1993). In this sub-population teetotalism was positively associated with incident type 2 diabetes, and much more common in those who drank <1 cup of coffee per day than in the others (Table 1 in the main article). Among the non-teetotallers, a low alcohol consumption was positively associated with incident type 2 diabetes, and more common in those who drank <1 cup of coffee per day than in the others. Thus, some of the negative association between coffee consumption and incident type 2 diabetes may be due to lower alcohol consumption in the reference group than in the other coffee groups. Adjusting for alcohol consumption (categorized into 7 groups: 0, 1, 2, 3-4, 5-8, and ≥9 times/month, and teetotallers) in addition to all of the other confounders in those screened after 1993, the relative risks for men and women together, any type of coffee, were raised from 0.87, 0.71, and 0.72, respectively, to 0.91, 0.75, and 0.74, in the three coffee groups (1-4, 5-8, and 9+). Thus, including alcohol in the main study would probably have weakened the estimated association between coffee and type 2 diabetes.

In general, we cannot rule out residual confounding as we have included a limited number of covariates, but it is difficult to tell how inclusion of several covariates would have affected the results. As a high coffee consumption seems to be associated with an unhealthy lifestyle (Table 1), the coffee-diabetes association might have been strengthened by adjusting for more lifestyle related variables. On the other hand, adjusting for alcohol would have weakened the coffee-diabetes association (see above).

Triglycerides and blood pressure

A high level of triglycerides is an established risk factor for type 2 diabetes, and it was strongly associated with incident type 2 diabetes in our study population (Table 1). A high coffee consumption was associated with smoking, low education and sedentary life style, which were all associated with high levels of triglycerides (data not shown), but still the level of triglycerides was lower in the highest coffee consumption group than in the reference group for men, and similar for women (Table 1). In the subgroup of male smokers with low education and low physical activity, the average triglyceride level in the four coffee groups was 2.97, 2.67, 2.35, and 2.33, respectively. The corresponding numbers in women were 1.85, 1.63, 1.52, and 1.58. For non-smokers with high education and high physical activity, there was almost no variation in triglyceride level over coffee groups (1.69, 1.71, 1.68, and 1.76 for men, and 1.08, 1.06, 1.04, and 1.06 for women). We cannot explain this life style dependent difference in the triglyceride-coffee association, but if the effect of coffee on diabetes was mediated through a lower level of triglycerides in the part of the population with an unhealthy lifestyle, where the diabetes incidence was highest, it would be wrong to adjust for triglyceride level, and we have not adjusted for it in the main article. On the other hand, there may be some unknown life style related background variables that affect both triglyceride level and coffee consumption, in which case triglycerides should be adjusted for. To some extent, the same argumentation holds for blood pressure. The effect of adjusting for these two factors, and for total cholesterol, is seen in eTable 2. After adjusting for triglycerides, the effect of additional adjustments for diastolic blood pressure and total cholesterol was very small.

Change in coffee consumption during follow up

In a subsample (n = 2354) of healthy individuals (no diabetes or cardiovascular history or hypertensive treatment at baseline) that were screened twice or more, with at least 6 years between the first and last screening, 1,356 reported a daily consumption of only boiled coffee at the first screening. At the last screening, 34% of these had switched to only other types. Correspondingly, out of 621 individuals who reported a daily consumption of only other types at the first screening, 15% had switched to only boiled coffee at the last screening. This change in coffee habits during follow-up may have blurred the distinction between the coffee types with regard to their association with type 2 diabetes. The subsample was mainly from the county Finnmark, which explains the high percentage drinking boiled coffee.

About 39% changed coffee group from the first to the last screening, 25% to a higher consumption group, and 14% to a lower consumption group. Roughly, 47% started and 1.6% stopped drinking coffee between the two screenings. More precisely: of the 143 which were in the reference group at the first screening, 67 (47%) were in another group at the last screening. Of the 2211 others, only 36 (1.6%) were in the reference group at the last screening. Thus, some of the individuals in the reference group of our study population were probably coffee drinkers during parts of the follow up time, which may have led to an underestimation of the association between coffee consumption and type 2 diabetes.

e**Table 2**. Adjusted relative risks (RR) for incident type 2 diabetes by coffee consumption, stratified on gender, for 170,729 men and 190,270 women with non-missing data for all variables adjusted for.

	Coffee consumption (cups/day)			
	<1	1-4	5-8	9+
Men and women, any type of coffee				
RR[a]	ref	0.76 (0.72-0.81)	0.66 (0.62-0.71)	0.80 (0.74-0.86)
RR[b]	ref	0.83 (0.78-0.89)	0.65 (0.60-0.69)	0.62 (0.58-0.68)
RR[c]	ref	0.88 (0.83-0.94)	0.73 (0.68-0.78)	0.73 (0.68-0.80)
RR[d]	ref	0.87 (0.81-0.92)	0.73 (0.68-0.78)	0.75 (0.69-0.82)
RR[e]	ref	0.87 (0.82-0.93)	0.73 (0.69-0.78)	0.76 (0.70-0.83)
N[f]	1,320 (3.5)	3,893 (2.7)	3,437 (2.5)	1,207 (3.0)
Men, any type of coffee				
RR[a]	ref	0.80 (0.74-0.87)	0.71 (0.66-0.78)	0.83 (0.76-0.92)
RR[b]	ref	0.86 (0.79-0.93)	0.69 (0.64-0.76)	0.67 (0.60-0.74)
RR[c]	ref	0.89 (0.82-0.97)	0.76 (0.69-0.83)	0.76 (0.68-0.84)
RR[d]	ref	0.88 (0.81-0.96)	0.76 (0.69-0.83)	0.78 (0.70-0.86)
RR[e]	ref	0.89 (0.81-0.97)	0.76 (0.70-0.83)	0.78 (0.70-0.87)
N[f]	734 (4.3)	2161 (3.5)	2148 (3.2)	853 (3.5)
Women, any type of coffee				
RR[a]	ref	0.71 (0.65-0.78)	0.59 (0.54-0.65)	0.76 (0.67-0.87)
RR[b]	ref	0.79 (0.72-0.87)	0.59 (0.53-0.65)	0.57 (0.50-0.66)
RR[c]	ref	0.86 (0.78-0.94)	0.70 (0.63-0.78)	0.70 (0.61-0.80)
RR[d]	ref	0.84 (0.77-0.93)	0.70 (0.63-0.78)	0.72 (0.63-0.83)
RR[e]	ref	0.85 (0.77-0.93)	0.71 (0.64-0.78)	0.73 (0.63-0.83)
N[f]	586 (2.8)	1732 (2.1)	1289 (1.8)	354 (2.2)
Men and women, boiled coffee[g]				
RR[a]	ref	0.88 (0.81-0.96)	0.69 (0.63-0.75)	0.85 (0.76-0.96)
RR[b]	ref	0.86 (0.79-0.94)	0.65 (0.59-0.71)	0.64 (0.56-0.73)
RR[c]	ref	0.89 (0.81-0.97)	0.69 (0.63-0.76)	0.74 (0.65-0.84)
RR[d]	ref	0.88 (0.80-0.96)	0.69 (0.63-0.76)	0.75 (0.66-0.85)
RR[e]	ref	0.88 (0.81-0.96)	0.70 (0.63-0.77)	0.76 (0.67-0.87)
N[f]	1320 (3.5)	902 (3.3)	797 (2.7)	333 (3.3)
Men and women, other types of coffee[h]				
RR[a]	ref	0.74 (0.69-0.79)	0.65 (0.61-0.7)	0.77 (0.70-0.84)
RR[b]	ref	0.84 (0.78-0.90)	0.66 (0.61-0.71)	0.61 (0.55-0.67)
RR[c]	ref	0.89 (0.83-0.95)	0.75 (0.7-0.81)	0.73 (0.66-0.80)
RR[d]	ref	0.87 (0.81-0.93)	0.75 (0.70-0.80)	0.75 (0.68-0.82)
RR[e]	ref	0.87 (0.82-0.93)	0.75 (0.7-0.81)	0.75 (0.68-0.83)
N[f]	1320 (3.5)	2717 (2.6)	2286 (2.4)	722 (2.8)

[a]Adjusted for year of birth and gender.
[b]In addition adjusted for BMI, smoking, education, and physical activity
[c]In addition adjusted for log(triglycerides)
[d]In addition adjusted for diastolic blood pressure
[e]In addition adjusted for total cholesterol
[f]Number (percentage) of incident type 2 diabetes cases.
[g]Excluding subjects with a daily consumption of ≥ 1 cup of other types of coffee than boiled
[h]Excluding subjects with a daily consumption of ≥ 1 cup of boiled coffee

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