

Serum HDL cholesterol was positively associated with cheese intake in the Oslo Health Study

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ABSTRACT

We have examined the association between cheese intake and serum lipids in the cross-sectional Oslo Health Study (18,770 subjects), using ANOVA and linear regression. In both sexes and in most of four age groups, i.e. young (30 years), middle-aged (40 and 45 years), seniors (50-60) and old (75-76 years), cheese intake was negatively associated with triglycerides and positively with HDL ($P < 0.05$ for trend). In the whole material, HDL was 1.38 (1.36-1.40), 1.44 (1.42-1.45), 1.50 (1.49-1.51) and 1.57 (1.56-1.58) mmol/L in cheese intake group 1-4 (i.e. intake 0.5, 2.0, 5.0 or 10.5 times per week). Corresponding values for triglycerides were: 1.79 (1.73-1.86), 1.67 (1.63-1.71), 1.57 (1.54-1.61) and 1.48 (1.46-1.50). Also in multiple linear regression analysis with several confounding variables the serum HDL vs. cheese intake association still prevailed ($P=0.001$), but the cheese vs. triglyceride association was not significant in the multivariate model.

Practical applications: The finding that cheese intake is positively and independently associated with serum HDL in men and women across a wide age range, and negatively with serum triglycerides, raises the question of whether our dietary guidelines might have focused too much on negative effects of saturated fat whereby possible positive effects of cheese may have been overlooked. The results invite new experimental studies on the more comprehensive effects of cheese, butter and milk on blood lipids, apolipoproteins and coagulation factors.

Keywords: HDL-cholesterol, triglycerides, cheese intake, men, women, cross-sectional study

Introduction

Although intake of saturated fats may raise serum cholesterol (Chi et al. 2004; Hegsted et al., 1965) the results seem to be ambiguous as regards the association between intake of milk fat and serum lipids. For example, (Chi et al., 2004) concluded that consumption of milk and milk products may have an unfavourable effect on hypercholesterolemia in the Japanese population. On the other hand, it has been reported that intake of cheese might not have adverse effects on the serum lipids (Colquhoun et al., 2003), and that cheese may be less cholesterol increasing than butter (Biong et al., 2004; Nestel et al., 2005; Tholstrup et al., 2004). Indeed, the question has been raised whether there might be a hypocholesterolemic factor in milk products (Eichholzer and Stahelin, 1993) and whether cheese intake might be beneficial in hyperlipidaemic patients (O'Callaghan et al., 1996).

The purpose of the present study was to examine the association between self-reported cheese intake frequency, and serum triglycerides and HDL cholesterol in the cross-sectional Oslo Health study.

Material.s/subjects and methods

Main project

In 2000-2001 the Oslo Health Study was conducted under the joint collaboration of the National Health Screening Service of Norway (now the Norwegian Institute of Public Health), the University of Oslo and the Municipality of Oslo. The study population included all individuals in Oslo County born in 1970, 1960, and 1955, 1940-41 and 1924-25. At the time of the data collection, the subjects were 30, 40, 45, 59-60, or 75 - 76 years of age. A total of 18,770 individuals (45.9% of the invited) participated. The responders consisted of 8,404 men (42.4% of the invited) and 10,366 women (49.3% of the invited)

who attended the physical examination and/or filled in at least one of the questionnaires. The response rate did not seem to be related to self-reported health, smoking, BMI or mental health as the participants differed only slightly from estimated prevalence values in the target population (Sogaard et al., 2004).

One self-administered questionnaire was part of the letter of invitation, whereas two supplementary questionnaires were handed out at the screening units, and sent back in pre-stamped self-addressed envelopes. The questionnaires provided information on health status, symptoms, diseases and various aspects of health related behaviour. Up to two reminders were sent to the non-responders. The second reminder invited those living in the suburban parts of the city to mobile screening units parked in the neighbourhood of the invited.

At the screening station a simple physical examination was conducted: A venous non-fasting blood sample was analyzed for serum total cholesterol (mmol/l), HDL cholesterol (mmol/l), glucose (mmol/l) and triglycerides (mmol/l). Low density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula (Friedewald et al., 1972). Automatic device (DINAMAP) measured pulse recordings, systolic- and diastolic blood pressures. Body weight (in kilograms), height (in cm) and waist-hip-ratio (cm) were measured with a standard procedure according to the protocol.

For further details, see: <http://www.fhi.no/hubro>. The study protocol was placed before the Regional Committee for Medical Research Ethics and approved by the Norwegian Data Inspectorate. The study has been conducted in full accordance with the World Medical Association Declaration of Helsinki.

Study sample for the present analyses

This study involved all four age groups, i.e. 30, 40 and 45, 59-60, and 75 - 76 years of age at inclusion. It was required that all subjects had data on the intake frequency of cheese, as well as on the serum HDL cholesterol (HDL) and triglyceride (TG) concentration. Of the 18,770 participants in the study there were 17,717 respondents (7,887 men and 9,830 women) having the required data, and this material was used in the present analyses.

The question concerning cheese intake was: "How often do you usually eat cheese (all kinds), with 6 response alternatives: seldom/never, 1-3 times per month, 1-3 times per week, 4-6 times per week, 1-2 times per day, 3 times or more per day. For table 1, the mid-point in each interval was used and the frequency time unit standardised to times per day. In the subsequent analyses, frequency of intake was grouped into four levels: \leq 1-3 times per month (855 men, 718 women); 1-3 times per week (2132 men, 1914 women); 4-6 times per week (2162 men, 2533 women); and \geq 1-2 times per day (2738 men, 4665 women). Cheese intake frequencies were calculated to obtain the same approximate unit, i.e. times per week: 0.5, 2.0, 5.0 and 10.5.

Statistical. analysis

The distributions of HDL and TG were positively skewed and their natural logarithms were used in analyses. In Table 2, the association between intake frequency of cheese (four levels), and HDL and triglycerides were estimated in each group by exponenting the mean logarithmic terms of the clinical measures. Linear trends were analyzed using one-way ANOVA. The relationship between serum HDL (and triglycerides) and cheese intake frequency was also explored using linear regression. The main focus was on changes in the beta coefficients for the HDL vs. cheese association when adding

additional variables. Cheese intake frequency was included with the 4 levels referred to above. The other independent variables were: sex, age group (as defined above), time since last meal., coffee intake (number of cups per day), intake frequency of other diet items (fruit/berries, fruit juice, fatty fish; with the same 6 levels as for cheese intake), use of cholesterol lowering drugs (never/now), frequency of alcohol intake the last year (8 levels: 4-7 times per week, 2-3 times per week, about once a week, 2-3 times per month, approximately one time per month, a few times in the last year, have not drunk alcohol the last year, have never drunk alcohol), smoking (now/never or previous), body mass index (kg/m^2), years at school, light physical activity at leisure time (with 4 levels: no activity, <1 hour per week, 1-2 hours per week, ≥ 3 hours per week), and birthplace (born in Europe or North America vs. born in a developing country, i.e. in Middle- or South-America, Asia, or Africa).

Four linear regression models were used to study the HDL (TG) vs. cheese associations; Model 1: Adjusted for sex and age group; Model 2: Model 1 + adjustments for frequency intake of fruit/berries, fruit juice, fatty fish (6 frequency levels), coffee intake (cups per day), and time since last meal (hours); Model 3: Model 2 + adjustments for frequency of alcohol intake the last year (8 frequency levels); Model 4: Model 3 + adjustments for smoking (Current, previous, never), body mass index (kg/m^2), physical activity (4 levels); Model 5: Model 4 + years at school, birthplace (Europe/North America vs. other). SPSS 15.0 was used for the statistical analyses. The significance level was $\alpha=0.05$.

Results

Intake frequency of cheese in four age groups of men and women

There was a monotonous increase in the mean intake frequency of cheese with increasing age group (Table 1). For all age groups, the mean cheese intake frequency was significantly ($P<0.01$) different from the other age groups, with one exception: the intake did not differ between middle-aged and senior men. In all age groups the mean intake frequency of cheese was higher in women than in men ($P<0.001$). In the whole material, there was a main effect of age ($F=173.3$, $P<0.001$) and sex ($F=314.2$, $P<0.001$), but no significant interaction between these variables.

Cheese intake frequency vs. serum HDL and triglycerides concentrations, by sex and age.

To explore the consistency of the cheese intake vs. serum lipid association we studied the relationship for each sex and age group separately (Table 2). For women there was a significant negative association between the intake frequency of cheese and serum triglycerides, and a positive relationship with serum HDL, observed in all age groups ($P<0.001$ for trend). The exception was found in young women. The cheese vs. triglyceride association was significant for middle-aged and senior men, but not for young and old men; the cheese vs. HDL association in men was significant in all age groups, except in old men (Table 2).

Association between serum lipids and cheese intake as studied by linear regression

HDL was positively associated with cheese intake frequency, irrespective of including many potential confounders ($P<0.001$, Table 3). The association was progressively weakened by adding potential confounders, and alcohol had the strongest attenuating

influence (Model 4 compared with Model 3). The negative association between serum triglycerides and cheese intake did not attain statistical significance when tested in Model 5 (13 independent variables included).

Discussion

This cross-sectional analysis of the Oslo Health Study shows that increasing frequency of cheese intake was positively associated with the serum HDL cholesterol level, and inversely so with serum triglycerides. The associations were fairly robust across age and sex groups, and remained significant even after adjusting for a number of possible confounding factors known to be associated with the HDL cholesterol and serum triglyceride level. There may be residual confounding by other dietary and lifestyle factors affecting the association, but it is difficult to see how these results can emerge from systematic errors such as information and selection bias. The method of categorising the exposure, frequency of cheese intake, will only give a rough estimate of the true total intake. However, single food frequency questions have been shown to rank individuals on total intake (Andersen et al., 2002).

The sera were from non-fasting subjects, and one would expect a large variation in the serum triglyceride concentration since chylomicron triglycerides might be present in various amounts. It is unlikely that these latter triglycerides have a major impact on the cheese and blood lipid association since including 'time since last food intake' as a confounding variable did not change the estimates in the linear regression model. The estimated LDL cholesterol levels based on Friedewalds formula (Friedewald et al., 1972) in sera from non-fasting subjects would also introduce erroneous results due to a larger random error, but are less likely to be systematically wrong. Additionally, self reported dietary exposure variables are likely to exert a considerable random error, implying that

the observed associations may be larger than those reported here. One issue not addressed in this analysis is the possible intake of low-fat cheese, but the amount is assumed to be low and not likely to affect the results.

The findings in this report are seemingly in contrast with our knowledge concerning dietary fat and blood lipids, and consequently also with current dietary guidelines. Cheese is listed as a major source of saturated fat in the American diet, and the guidelines published in 2005 emphasise the need to reduce the intake of saturated fat, *trans* fat and dietary cholesterol (Dietary Guidelines for Americans, 2005). The literature concerning the effect of cheese intake on blood lipids however, is less consistent than what would be expected from the guidelines, and even more so when addressing the risk of coronary heart disease.

Cheese fat and blood lipids

Consumption of milk and milk products has been reported to be positively associated with serum total cholesterol, LDL cholesterol and HDL cholesterol (Chi et al., 2004). Several intervention studies have shown that diets containing low-fat dairy products are associated with favourable changes in serum cholesterol (Marckmann et al., 1994; Sandstrom et al., 1992; Schuster et al., 1980; Seidel et al., 2005). Conversely, diets rich in saturated fat have been regarded to contribute to the development of coronary heart diseases, weight gain and obesity (Insel et al., 2004).

It seems, however, that fat consumption from cheese may have different effects on serum lipids than could be expected from the fat content, especially when compared to

other dairy fat products such as milk and butter (Eichholzer and Stahelin, 1993). A detailed discussion on possible mechanisms falls beyond the scope of this paper, but we will shortly summarize some issues concerning dietary fat and blood lipids which may be relevant for further research

Saturated fatty acids

Saturated fatty acids provide more than half of the cheese fatty acids (USDA National Nutrient Database for Standard Reference, 2007a). The various saturated fatty acids differ in their physiological effects (Grundy, 1994; Henry et al., 2002; Schuster et al., 1980; Sun et al., 2003). For example, lauric acid (12:0) may have antiviral and antibacterial functions, and may inhibit cyclooxygenase (Henry et al., 2002). Lauric-, myristic (14:0) and palmitic (16:0) acid may raise both LDL- and HDL cholesterol, whereas stearic acid (18:0) is inert with regard to total serum cholesterol concentration, and considered non-atherogenic (Grundy, 1994).

Unsaturated fatty acids

Oleic acid (18:1c9) is the major unsaturated fatty acid in milk fat, constituting approximately 90% of the unsaturated fatty acids, and 26% of total fatty acids; one litre of whole milk provides 8 g oleic acid (USDA National Nutrient Database for Standard Reference, 2007a). Hence, cheese and other dairy products contribute substantially to this fatty acid in many countries; providing for example about 25% of the average daily intake in Norway (*Utviklingen i norsk kosthold* (The development in Norwegian nutrition) 2007b). A high intake of monounsaturated fatty acids may lower both plasma total and LDL cholesterol, and may also reduce the triglyceride concentrations (Kris-Etherton et al., 1999).

Dairy fat and cardiovascular disease

To our knowledge, epidemiological cohort studies do not show a higher risk for coronary heart diseases in persons with high intakes of dairy fat, as also suggested by (Elwood et al., 2004). On the contrary, several studies have found a lack of association between milk consumption and CHD (Fehily et al., 1993; Ness et al., 2001; Stahelin et al., 1992; Willett et al., 1993). For example, in two Swedish studies cardiovascular risk factors were negatively associated with the intake of milk fat (Smedman et al., 1999; Warensjo et al., 2004). To what extent these results were confounded by the frequency of cheese intake is not known, but one might assume that a high intake of milk would also be associated with a high intake of cheese.

A Norwegian study suggests that intake of dairy products may protect against myocardial infarction (MI) by mechanisms not related to total serum cholesterol (Biong, 2007). Interestingly, (Sjogren et al., 2004) reported that intake of fatty acids typically found in milk products was associated with a more favourable LDL profile in healthy men, i.e. a decreased abundance of the atherogenic, small, dense LDL particles (sdLDL). A Canadian 13 year follow-up study analysed plasma LDL distribution and showed that cardiovascular risk was largely related to accumulation of sdLDL (St-Pierre et al., 2005). These particles are associated with hypertriglyceridemia and insulin resistance (Picard, 1995), the metabolic syndrome and increased risk for CHD (Lamarche et al., 1999; Tonstad and Hjermann, 2003). Recently, Elwood and co-workers (Elwood et al., 2007) reported that consumption of milk and dairy products was associated with reduced prevalence of the metabolic syndrome.

Both the lipoprotein pattern and blood coagulation tendency are essential for developing myocardial infarction, and cheese fatty acids could in theory influence both processes. Furthermore some saturated fatty acids may increase both LDL and HDL

cholesterol. It seems that the balance between these lipoproteins is crucial as regards coronary risk. It was shown by Høstmark et al. (Hostmark et al., 1990)) that an index reflecting the LDL/HDL balance,

$$\text{ATH-index} = (\text{total cholesterol} - \text{HDL}) * \text{apoB} / (\text{apoA} * \text{HDL})$$
, improved the discrimination between controls and subjects with coronary artery stenosis, whereas the distribution of total cholesterol was similar in controls and patients. In keeping with these early results, in the INTERHEART case-control study on risk factors associated with myocardial infarction in 52 countries, an increase in apo B/apo A1 ratio was shown to be the strongest risk factor for myocardial infarction (Yusuf et al., 2004).

The studies referred to above seem to suggest that a moderate intake of cheese fat might not have negative effects on the distribution of the apolipoproteins, and one may also speculate that cheese could contain non-lipid factors which could have beneficial effects upon the serum lipids. Hypothetically, such factors could possibly be produced by the lactic bacteria in cheese (Fonden, et al., 2003).

In conclusion, our results show that the intake frequency of cheese can be positively associated with serum HDL cholesterol, and negatively with serum triglycerides, but the data do not clarify whether the associations are causal. The association between cheese intake and serum HDL also prevailed in multivariate analyses involving a large number of variables. The results raise the question whether our dietary guidelines might have focused too much on separate effects of saturated fat whereby possible positive effects of cheese may have been overlooked. The findings invite new experimental studies on the more comprehensive effects of cheese, butter and milk on blood lipids, apolipoproteins and coagulation factors.

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TABLE 1.

MEAN (SD) FREQUENCY OF CHEESE INTAKE (TIMES/ DAY) BY SEX AND AGE IN THE OSLO HEALTH STUDY (N=17,717).

	Men			Women		
	n	Mean	SD	n	Mean	SD
All	7887	1.1	0.9	9830	1.3	0.9
30 years	1767	0.9	0.8	2169	1.1	0.9
40 + 45 years	2791	1.0	0.9	3513	1.3	0.9
59-60 years	2002	1.1	0.9	2257	1.4	0.9
75-76 years	1327	1.3	0.9	1891	1.6	0.9

For all age groups of men and women, the mean cheese intake frequency was significantly ($P < 0.01$) different from the other age groups, with one exception: the intake did not differ in middle-aged and senior men. Women had higher intake than men, found in all age groups.

TABLE 2.
 GEOMETRIC MEAN¹ (SD²) OF HIGH DENSITY LIPOPROTEIN CHOLESTEROL (HDL) AND TRIGLYCERIDES (TG) ACROSS INCREASING FREQUENCY OF CHEESE INTAKE³ IN THE OSLO HEALTH STUDY (N=17 717).

		N ³	Grouped frequency of cheese intake				P for trend
			≤3 times/ month	1-3 times/wk	4-6 times/wk	≥Once/day	
HDL, mmol/L							
Men	30 years	1767	1.18 (0.29)	1.20 (0.28)	1.24 (0.30)	1.23 (0.29)	0.016
	40 + 45 years	2791	1.17 (0.31)	1.22 (0.31)	1.25 (0.32)	1.27 (0.34)	<0.001
	59-60 years	2002	1.24 (0.37)	1.33 (0.38)	1.33 (0.36)	1.36 (0.40)	<0.001
	75-76 years	1327	1.36 (0.37)	1.34 (0.45)	1.41 (0.43)	1.39 (0.41)	0.233
Women	30 years	2169	1.47 (0.35)	1.52 (0.36)	1.56 (0.36)	1.59 (0.37)	<0.001
	40 + 45 years	3513	1.46 (0.41)	1.50 (0.40)	1.56 (0.38)	1.57 (0.39)	<0.001
	59-60 years	2257	1.49 (0.39)	1.61 (0.44)	1.63 (0.46)	1.71 (0.46)	<0.001
	75-76 years	1891	1.51 (0.42)	1.62 (0.47)	1.69 (0.51)	1.69 (0.46)	<0.001
TG, mmol/L							
Men	30 years	1767	1.61 (1.39)	1.49 (1.16)	1.51 (1.11)	1.46 (0.91)	0.066
	40 + 45 years	2791	1.86 (1.76)	1.76 (1.58)	1.63 (1.36)	1.61 (1.20)	<0.001
	59-60 years	2002	1.69 (1.04)	1.67 (1.13)	1.65 (1.35)	1.55 (0.97)	0.031
	75-76 years	1327	1.36 (0.71)	1.54 (1.15)	1.44 (0.98)	1.50 (0.87)	0.113
Women	30 years	2169	0.99 (0.62)	1.00 (0.84)	0.96 (0.66)	0.93 (0.60)	0.089
	40 + 45 years	3513	1.21 (1.07)	1.14 (0.91)	1.05 (0.78)	1.03 (0.75)	<0.001
	59-60 years	2257	1.48 (1.29)	1.37 (1.03)	1.35 (0.88)	1.21 (0.80)	<0.001
	75-76 years	1891	1.68 (1.00)	1.49 (0.82)	1.44 (0.84)	1.42 (0.91)	<0.001

¹ Analyzed using the natural logarithm of the laboratory variables and exponentiating the resulting mean logarithmic term.

² SD of untransformed variable

³ Total numbers of subjects in each age group; the number of subjects in cheese intake levels

1-4 were, *men*: age 30 years: 201, 578, 567, 421; 40+45 years: 328, 757, 776, 930; 59-60

years: 223, 525, 515, 739; 75-76 years: 103, 272, 304, 648. Corresponding numbers for

women: 180, 585, 641, 763; 281, 711, 921, 1600; 166, 405, 551, 1135; 91, 213, 420, 1167.

TABLE 3:

LINEAR REGRESSION MODELS FOR THE ASSOCIATION BETWEEN SERUM HDL (TRIGLYCERIDES, TG) AND INTAKE FREQUENCY OF CHEESE (4 LEVELS), AS INFLUENCED BY OTHER FACTORS (N= 17,717)

	HDL, mmol/L			TG mmol/L		
	B(SE)	Beta	P	B(SE)	Beta	P
Model 1	0.035(0,003)	0,081	<0,001	-0,079(0,008)	-0,071	<0,001
Model 2	0.031(0,003)	0,072	<0,001	-0,057(0,009)	-0,051	<0,001
Model 3	0,023(0,003)	0,053	<0,001	-0,048(0,009)	-0,044	<0,001
Model 4	0,013(0,003)	0,030	<0,001	-0,024(0,009)	-0,021	0,008
Model 5	0,012(0,003)	0,028	<0,001	-0,016(0,009)	-0,014	0,102

1 Grouped frequency of cheese intake: Level 1: ≤ 0.5 times/week; Level 2: 2 times/week; Level 3: 5 times/week; Level 4: ≥ 10.5 times/day

Model 1: Adjusted for sex and age group

Model 2: Model 1 + adjustments for frequency intake of fruit/berries, fruit juice, fatty fish (6 frequency levels), coffee intake (cups per day), and time since last meal (hours)

Model 3: Model 2 + adjustments for frequency of alcohol intake the last year (8 frequency levels)

Model 4: Model 3 + adjustments for smoking (Current, previous, never), body mass index (kg/m^2), physical activity (4 levels)

Model 5: Model 4 + years at school (6 levels), birthplace (Western country, other)

