GÖTEBORGS
UNIVERSITET

EFFECTS OF MILK WITH VARIOUS FAT CONTENT ON BLOOD LIPID LEVELS IN HUMANS : A SYSTEMATIC REVIEW

Patrik Hansson
Erik Hulander

Examensarbete 15 hp
Dietistprogrammet 180/240 hp
Handledare: Fredrik Bertz, Lasse Ellegård
Examinator: Heléne Bertéus Forslund
2009-05-20

Sahlgrenska Academy
at University of Gothenburg
Department of Clinical Nutrition

Abstract

Title: Effects of milk with various fat content on blood lipid levels in humans: A systematic review

Authors: Patrik Hansson, Erik Hulander

Supervisor: Fredrik Bertz, Lasse Ellegård
Examiner: Heléne Bertéus Forslund
Programme: Dietician study programme, 180/240 hp
Type of paper: Examination paper, 15 hp
Date: May 20, 2009

Background
Cardiovascular disease is a common cause of death in Western society. Independent risk factors include high blood lipid levels. Milk is rich in saturated fatty acids, expected to induce raised LDL-levels. General recommendations are to avoid high fat milk products.

Objective
To examine documented effects of milk with various fat content on blood lipid levels in humans.

Search strategy
Original articles were collected through searches in *Pubmed* and *Scopus*.

Selection criteria
Inclusion criteria were human subjects, articles written in English, Western study populations (or Western descendants) and that supplementation was of milk only. Exclusion criteria were milk not from cow, enriched or otherwise modified milk and study periods for less than three weeks. Studies involving patients with manifested gastrointestinal disease were also excluded.

Data collection and analysis
In total, eight studies were reviewed, analysed and evidence graded according to *GRADE*.

Main results
The studies held a great variation in terms of evidence grade. Only one randomized controlled trial could be found, several studies proved to have very low evidence grade. Two studies showed a decrease in blood lipid levels and one an increase in triglyceride levels. Overall, there was no coherent effect on blood lipid levels.

Conclusions
This systematic review article fails to find evidence that milk, independent of fat content, affects examined blood lipid levels. The power of identifying an effect from milk, assuming there is one, is low due to halting study designs.

Sahlgrenska Akademin
vid Göteborgs universitet
Avdelningen för klinisk näringslära

Sammanfattning

Titel: Effekter av mjölk med olika fetthalt på blodlipidnivåer hos människor : En systematisk översikt

Författare: Patrik Hansson, Erik Hulander

Handledare: Fredrik Bertz, Lasse Ellegård
Examinator: Heléne Bertéus Forslund
Linje: Dietistprogrammet, 180/240 hp
Typ av arbete: Examensarbete, 15 hp
Datum: 2009-05-20

Bakgrund
Hjärt- och kärlsjukdom är en vanlig dödsorsak i den västerländska världen, där höga blodfetter är en oberoende riskfaktor. Mjölk är rikt på mättade fettsyror som förväntas höja LDL-nivåerna. Generella rekommendationer är att undvika feta mjölkprodukter.

Syfte
Att undersöka dokumenterade effekter av mjölk med olika fetthalt på blodlipidnivåer i människor.

Sökväg
Originalartiklar samlades in från sökningar i *Pubmed* och *Scopus*.

Urvalskriterier
Inklusionskriterer var humanförsök, artiklar på engelska, västerländska studiepopulationer (eller ättlingar därav) samt supplementering gällande endast mjölk. Exklusionskriterier var icke komjölk, berikad eller på andra sätt modifierad mjölk samt interventionsperioder kortare än tre veckor. Studier där patienter utvecklat gastrointestinala sjukdomar var också exkluderade.

Datainsamling och analys
Totalt åtta studier valdes ut, granskades och evidensgraderades enligt *GRADE*-skalan.

Resultat
Evidensgraden varierade mycket mellan ingående studier. Endast en studie var RCT och flertalet övriga studier hade mycket låg evidensgrad. Två studier visade på sänkta blodlipidnivåer och en studie visade på en ökning av triglycerider. Sammanfattningsvis hittades inga entydiga effekter på blodlipidnivåer.

Slutsats
Denna systematiska översiktsartikel lyckas inte finna evidens för att mjölk, oberoende av fetthalt, påverkar undersökta blodlipidnivåer. Styrkan att identifiera en effekt av mjölk, om det finns någon, är låg på grund av svagheter i ingående studier.

Table of contents

Abbreviations

CVD	Cardiovascular Disease
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
NNR	Nordic Nutrition Recommendations 2004
RCT	Randomized Controlled Trial
TC	Total Cholesterol
TG	Triglycerides
VLDL	Very Low Density Lipoprotein

Introduction

Cardiovascular disease (CVD) alone is the dominating single cause of death in Sweden, accounting for well over 40 percent of all deaths (1). Independent risk factors for developing CVD include high blood lipid levels. A serum Total Cholesterol (TC) value above 5 mmol/l, Low Density Lipoprotein (LDL) value above 3 mmol/l, High Density Lipoprotein (HDL) below 1 mmol/l and Triglycerides (TG) above 2 mmol/l indicate increased risk of developing CVD (2).

Epidemiological studies show a correlation between hyperlipidaemia and increased incidence of CVD (3). A large proportion of the Swedish population, about 70%, suffers from hyperlipidaemia (TC above 5 mmol/l). Older population segments have shown to have an even higher prevalence, with numbers reaching up to 90% of those aged 50-70 years (4).

Hyperlipidaemia can be prevented through a healthy lifestyle and a well balanced diet. Recommendations for this include increased intake of vegetables and fruits, good fat quality and regular physical activity as well as absence from smoking (4).

Milk contains a high degree of saturated fatty acids that are expected to induce raised LDL levels (5,6). Average liquid milk intake in Sweden amounts to 0.2 litre per day among women and 0.3 litre per day among men, with a majority consuming 1.5 percent fat milk. In the average Swedish diet this accounts for about five percent of total fat intake for both men and women (7).

Proteins in milk products have shown to have a postprandial insulinotropic effect exceeding what would be expected based on carbohydrate contents (8,9). Insulin lowers synthesis of Very Low Density Lipoprotein (VLDL), a lipoprotein fraction that later turns into LDL cholesterol (10).

Nordic Nutrition Recommendations states that low fat dairy products should be preferred to whole fat milk products, since saturated fat in milk products are expected to raise blood lipid levels (11,12).

Research questions

Based on the expected hyperlipidemic effect of saturated fat along with a possible hypolipidemic effect from insulin, what is the outcome from milk consumption on blood lipid levels? Does fat content in milk matter and could there be a beneficial effect from low fat milk?

Aim

The aim of this systematic review article is to examine documented effects of milk with various fat content on blood lipid levels.

Method

Data was collected through searches in *Pubmed* and *Scopus*. Date for collection of studies was 27th February 2009. Database searches are shown in Table 1 below.

Table 1, Database searches

Database	Search query
Scopus	*TITLE(milk AND effect AND NOT soy AND NOT enriched AND NOT modified AND NOT plant AND "randomized controlled trial" OR "clinical trial" OR "controlled trial" AND human) AND TITLE-ABS-KEY(cholesterol) AND (LIMIT-TO(LANGUAGE,"English")) AND (LIMIT-TO(DOCTYPE,"ar"))*
Pubmed	*"milk"[Title] AND "effect"[Title] NOT "soy"[Title] NOT "enriched"[Title] NOT "modified"[Title] NOT "plant"[Title] AND "cholesterol"[Title/Abstract]* Limits: RCT, Clinical Trial, human, English

Inclusion & exclusion criteria

Inclusion criteria were human subjects, articles written in English, Western study populations (or Western descendants) and that supplementation was of milk only. Exclusion criteria were milk not from cow, enriched or otherwise modified milk and study periods for less than three weeks. Studies involving patients with manifested gastrointestinal disease were also excluded.

Study selection

The search query in Scopus gave 167 matches. Out of these, 109 were animal studies, 29 examined modified cow milk and 14 studied fermented products. Three were based entirely upon Japanese subjects, two did not examine cholesterol levels. One did not include healthy subjects and two were not relevant due to short study periods. Thus, seven articles from Scopus were included in this review.

The search query in PubMed gave 11 matches. Out of these five examined fermented products, another three looked at specific milk constituents only. One study was performed on Japanese subjects only. From the two studies left one had already been included from Scopus. Hence, the Pubmed search gave one more study. Altogether this review is based upon eight original study articles.

Data processing and analysis

Analysis and grading of studies was performed according to suggested guidelines defined in the *GRADE* system (13). According to *GRADE*, there are four different grades of evidence: very low, low, moderate and high. End points analysed were TC, HDL, LDL and TG.

Results

Below are descriptions of selected studies and associated evidence grades. Results from study interventions are displayed in Table 2.

Hepner et al, 1979 (14)

Study design: The study included two separate experiments. One was divided into two subgroups (I_{1a} and I_{1b}) and had a parallel non-randomized uncontrolled design. The other experiment included an intervention group (I_2) and a control group that was followed up for half of the study period. No simultaneous data from the intervention group was declared for comparison to the control group. Laboratory data from the control group was reported every other week, while data from the intervention group was displayed as a mean value of the intervention period. Study design for this experiment was non-randomized and uncontrolled.

Intervention: I_{1a} and I_{1b} was told to consume an additional amount of 0.72 litre 2% fat milk for four weeks. I_2 was to consume the same amount for 12 weeks.

Habitual milk intake: No information given.

Participants: All were to be in good general health with no history of cardiovascular, cerebrovascular or gallbladder diseases. Participants weights were not to be more than two standard deviations above the mean for their age and height. Neither were they to be indulged in any weight-reducing or low-fat diets.

Number of participants: I_{1a} was composed of six men and four women while I_{1b} was made up of five men and three women. I_2 consisted of three men and seven women.

Mean age: I_{1a} : 26 ± 3 years, I_{1b} : 27 ± 4 years, I_2 : 37 ± 12 years.

Evidence grade: Very low

Hussi et al, 1981 (15)

Study design: The study, which took place in a prison, was a non-randomized controlled trial and consisted of one intervention group (I) and one control group (C). Allocation into groups was determined by habitational blocks within the prison and therefore not randomized.

Intervention: Subjects in the intervention group consumed 2.7 litres of 0.05% fat milk, compared to the control group which consumed less than 0.3 litre of milk products per day. The two diets were formulated to contain the same relative proportions of macronutrients. The trial began with three weeks of control diet for both groups, followed by three weeks of intervention respective control diet.

Habitual milk intake: No information given.

Participants: Healthy male prisoners.

Number of participants: Intervention group was composed of 23 men while the control group was made up of 15 men.

Mean age: No information was given about mean age or age span.

Evidence grade: Low/Moderate

Rossouw et al, 1981 (16)

Study design: The study was a parallel randomized uncontrolled trial consisting of two intervention groups.

Intervention: There were two interventions, one group that consumed additional 2.0 litres of skim milk (I_1) and one group that consumed additional 2.0 litres of 3.3 % fat milk (I_2). Both interventions lasted for three weeks with a one week baseline before and a one week follow up after the intervention weeks.

Habitual milk intake: Both intervention groups had similar dietary fat and cholesterol intake. No information about the participants habitual milk intake was provided.

Participants: Healthy white boys.

Number of participants: I_1 was composed of eleven boys while I_2 was made up of 10 boys.

Mean age: No information given. Age span was 16-18 years.

Evidence grade: Low/Moderate

Thompson et al, 1982 (17)

Study design: The study was a non-randomized cross over with no wash out period.

Intervention: Participants were told to consume 1.25 litres of 2 % fat milk for three weeks and thereafter 0.25 litre of 2 % fat milk for another three weeks. No habitual milk intake was allowed during the interventions.

Habitual milk intake: Average milk intake was before the start of the study approximately 0.5 litre daily of mainly 2 % fat milk. Two individuals consumed more than 1 litre daily habitually and were therefore provided with 1.5 litres of 2 % fat milk during the first three weeks and 0.5 litre of 2 % fat milk for the next three weeks.

Participants: Healthy men and women with 99.5 ± 0.74 % of desirable weight.

Number of participants: 26 males and 42 females.

Mean age: 22 ± 4 years.

Evidence grade: Very low

Massey, 1984 (18)

Study design: The study was a non-randomized cross over.

Intervention: There were two interventions where all participants followed the same intervention at the same time. In the first intervention, participants were told to consume additional 0.72 litre of 2 % fat milk (with a total maximum intake of 1.92 litres per day) for three weeks in comparison to a three weeks long milk free period. In the second intervention, participants were told to consume additional 0.72 litre of skim milk (with a total maximum intake of 1.92 litres per day) for three weeks in comparison to another three weeks long milk free period. Because of bad compliance the additional skim milk intake was only to be 0.5 litre.

Habitual milk intake: Habitual milk intake ranged between zero to 2.16 litres per day. Milk consumption was monitored and mean intake was found to be 1.5 litres of 2% fat and 1.25 litres of skim milk during the additional periods.

Participants: Healthy normolipidemic males.

Number of participants: 32 males.

Mean age: No information given. Age span was 18-25 years.

Evidence grade: Very low

Buonopane et al, 1992 (19)

Study design: The study was a parallel non-randomized uncontrolled trial.

Intervention: Participants were allocated into three groups. One group for compensation of seasonal variation, another group composed of those with normal blood lipid levels and the third group made up of hyperlipidemics. The two intervention groups were told to consume additional 0.95 litre of fortified skim milk for eight weeks after a one week baseline period. Fortification consisted of solids from milk but not fat, hence protein and mineral content of the supplemental drink was more nutrient dense than normal milk.

Habitual milk intake: No information given.

Participants: No information given.

Number of participants: 82 subjects in total of which 18 (10 males and 8 females) were put in the seasonal index group. 64 test subjects (41 males and 23 females) of which 39 were hyperlipidemics and 25 were normolipidemics.

Mean age: Test groups were at the age of 55 ± 10 years. Seasonal index group was at the age of 43 ± 13 years.

Evidence grade: Low

Steinmetz et al, 1994 (20)

Study design: The study was a parallel randomized cross over.

Intervention: Participants were put on a controlled diet according to guidelines from American Heart Association (21). They were then randomly assigned to consume either 236ml/1000kcal of 0.2 % fat milk for six weeks or the same amount of 3.4 % fat milk for an equal period of time. After this first intervention period there was a wash out for 10-16 weeks before the groups switched interventions.

Habitual milk intake: No information given.

Participants: The study included only those with a bodyweight within 25% range of ideal and TC percentile between 25-90. No lactose intolerant or smoking subjects were allowed to participate. Subjects exhibiting extreme physical activity were excluded, as were recreational drug users.

Number of participants: 8 males.

Mean age: No information given. Age span was 20-36 years.

Evidence grade: Moderate

Barr et al, 2000 (22)

Study design: The study was a randomized controlled trial.

Intervention: Participants in the intervention group (I) were told to consume an additional amount of 0.71 litre of skim milk or 1 % fat milk daily for 12 weeks. Participants in the control group (C)

were told to continue with their habitual diet.

Habitual milk intake: No more than 0.36 litre of dairy products daily.

Participants: Inclusion criteria included habitual daily intake of maximum 0.36 litre dairy products and willingness to consume the additional amount of 0.71 litre of skim milk or 1 % fat milk. To be included in the study subjects needed to have a BMI in the range between 16 and 36. Female subjects needed to be at least five years post menopause. No calcium supplementation was allowed. Subjects medicated against hypertension or hyperlipidemia were to be on a stable dosage since at least four weeks prior to enrolment. Exclusion criteria included diabetics, chronic diseases, current hypertension and current hyperlipidemia.

Number of participants: Intervention group was composed of 35 men and 63 women while control group was made up of 36 men and 66 women.

Mean age: 65 ± 7 years in both groups.

Evidence grade: High

Intervention results

Table 2 below displays the effects of interventions in comparison to baseline values. Results from the study conducted by Steinmetz et al, a randomized cross over trial, are shown as the differences in effect between the two intervention periods. Complementary information regarding results from each intervention period is therefore also presented.

Steinmetz et al found a decrease in HDL-levels in both groups in comparison to baseline (-0.19 mmol/l for skim milk and -0.25 mmol/l for whole milk, $p<0.05$). TC decreased in both groups (-0.40 mmol/l for skim milk and -0.19 mmol/l for whole milk) but was only statistically significant in the skim milk group ($p<0.05$). A non-significant change compared to baseline for TG- and LDL-levels was found. TG-levels decreased (0.11 respectively 0.18 mmol/l) for skim and whole milk groups. LDL-levels decreased in the skim milk group by 0.19 mmol/l and increased in the whole milk group by 0.03 mmol/l. No statistically significant changes from baseline between groups was found, as displayed in Table 2.

Table 2. Study results - blood lipid changes after intervention

Author, year	Intervention	TC [mmol/l]	HDL [mmol/l]	LDL [mmol/l]	TG [mmol/l]	Evidence Grade
Hepner et al, 1979	I_{1ab} - 0.72 litre additional 2% fat milk, n = 17 I_2 - 0.72 litre additional 2 % fat milk, n = 10	I_{1a} :+0.23 I_{1b} :-0.21 I_2:-0.36	-	-	I_{1a}: +0.08 I_{1b}: +0,32** I_2: +0.09	Very low
Hussi et al, 1981	I - 2.7 litres of skim milk, n = 23 C - Max 0.3 litre milk products, n = 15	I: -0.08 C: +0.01	I: +0.03 C: -0.04	-	I: +0.09 C: +0.11	Low / Moderate
Rossouw et al, 1981	I_1 - 2 litres additional skim milk, n = 11 I_2 - 2 litres additional full cream milk, n = 10	I_1: -0.65** I_2: -0.08	I_1: -0.26* I_2: +0.05	I_1: -0.36* I_2: -0.03	I_1: -0.27** I_2: -0.26*	Low / Moderate
Thompson et al, 1982	I_1- 1.25 litres 2% fat milk, n = 68 I_2 -0.25 litre 2 % fat milk, n = 68	I_1: -0.1 I_2: +0.05	I_1: -0.03 I_2: +0.03	I_1: -0.05 I_2: +0.03	I_1: 0 I_2: -0.02	Very low
Massey, 1984	I_1 - 1,5 litres 2% fat milk, n = 21 I_2 - 1,25 litres skim milk, n = 21	I_1:+0.36 I_2:-0.1	-	-	I_1:+0.2 I_2:+0.08	Very low
Buonopane et al, 1992	I_1 - 0.95 litre additional fortified skim milk, n = 25 I_2 - 0.95 litre additional fortified skim milk, n = 39	I_1: -0.14 I_2: -0.4*	-	-	-	Low
Steinmetz et al, 1994	Either 0.2% or 3,4% milk in the quantity of 236ml/1000kcal, n = 8	I_Δ: -0.21	I_Δ:+0.07	I_Δ: -0.22	I_Δ:+0.07	Moderate
Barr et al, 2000	I - 0.71 litre additional skim or 1% fat milk, n = 98 C - Max 0.36 litre milk products, n = 102	I: -0.01 C: +0.06	I: -0.01 C: +0.04	I: -0.04 C: +0.03	I: +0.12 C: -0.03	High

I: Intervention groups
I_Δ: Difference in effect of skim milk supplementation, where basis for comparison is whole milk supplementation.
C: Control groups
*: $p < 0.05$
**: $p < 0.01$

Discussion

The studies we have examined fail to give convincing evidence that milk, independent of fat content, affect blood lipid levels.

Barr et al´s randomized controlled trial had the highest evidence grade and the largest study population. Participants habitual diet were to include maximum 0.36 litre of dairy products daily, which made a stable and reliable comparison to the intervention group possible. This study failed to show any effect from skim or low fat milk. However, results cannot be drawn on effects from amount of fat in low fat milk types as the number of subjects consuming skim versus 1% fat milk was not recorded.

Steinmetz et al did find a statistically significant difference after six weeks milk supplementation between skim and whole-milk, however similar differences were in place also before supplementation. Since study participants were put on a stringent controlled diet in adherence to recommendations by the *American Heart Association*, changes would be expected. It is difficult to draw conclusions regarding what effect milk itself has instigated since baseline. Change in effects of interventions, which is the one reliable comparable variable, was not found. This study included only 8 participants. The low participation number makes it hard to draw reliable conclusions about the results, as existing effects could have passed by unnoticed.

Rossouw et al found statically significant changes when adding high amounts of milk. No habitual diet was declared for the study population consisting of male teenagers. Decreases were recorded in all of our chosen end points in the skim milk group, albeit altering the lipid profile in an unfavourable way increasing the TC/HDL-ratio. These results are relevant since several studies only measures TC values without respect to different lipoprotein fractions. Examining those fractions gives a more complete perspective on the cholesterol lowering effect, showing possible negative health effects. The whole milk group showed decreased TG-levels but with a higher p-value than the skim milk group. Participants in this study drank 0.5 litre milk to each main meal and before bedtime, altogether consuming 2.0 litres daily. Since decreases in TC, HDL and LDL were only seen in the skim milk group, this indicates a support for the hypothesis of a postprandial insulinotropic effect from milk inhibiting VLDL-synthesis.

Results from Rossouw et al should be seen in the light of the study results found by Hussi et al who, under a controlled diet with a control group consuming no more than 0.3 litre of milk per day, failed to see statistically significant differences in any blood lipid levels. Rossouw et al and Hussi et al both had high amounts of milk consumption (2.0 litres respective 2.7 litres) during interventions and were given the same evidence grades. One could question whether amounts consumed in these two studies are clinically relevant for the average consumer, who typically have a considerably lower milk intake (7).

Buonopane et al did find a statistically significant difference in TC-levels in hyperlipidaemics. Since only TC was recorded, no conclusion can be drawn about implications on cardiovascular health predictors. This study intended to correct for seasonal changes by allocating participants in a non-randomized fashion into a seasonal index group. This group was in better health, exercised more and was taking less medications than intervention groups. No changes in the seasonal index group was found, ultimately this does not mean that no changes could have taken place in the intervention groups.

Hepner et al found a statistically significant increase in TG in one of the groups. This did however not follow through in any of the other groups, even though the same amount and type of milk was consumed during similar conditions. There was a large proportion of females in this study, a population who have shown to feature variations in TC with up to 0.5 mmol due to oestrogen level changes during the menstrual cycle (23). One could raise the question whether a study with only a small group of uncontrolled, non randomized participants with evidence grade very low is worth comparing to better designed studies.

The study done by Massey showed no effect from neither 2% fat milk nor skim milk when compared to a period with no milk intake. Only mean intake of milk during the different intervention periods were recorded. Therefore, no conclusions can be reached about contrasts in effect from various amounts of milk consumed within the intervention group. If effects were indeed to be divergent, they could be diluted beyond the extent of a measurable variation. What can be said, based upon the study design, is that adding skim or whole milk to a milk-free diet did not provide any statistically significant difference in TC nor TG. However, fat intake during the skim milk period was lower than during the no milk period. Unfortunately this study did not measure lipoprotein fractions, important changes in the ratio among these could have taken place unnoticed.

Thompson et al, who compared varying amounts of milk and blood lipid levels, found no relation between increased milk intake and change in blood lipid levels. There are however several sources of error in the study, a majority of participants were fertile females. No limitations were put on consumption of other milk products, one can therefore ponder the idea that increased milk intake could have resulted in spontaneously decreased intake of those, which could also affect blood lipid levels. There was no wash out separating the high and low milk diet, which means that the low milk diet was compared to results of the end of a high milk diet. This makes it hard to conduct a fair comparison of the two interventions. What can be said is that no difference could be seen in changes between high milk intake compared to baseline and low milk intake compared to high milk intake.

Conclusion

This systematic review article fails to find evidence that milk, independent of fat content, affect examined blood lipid levels. The power of identifying an effect from milk, assuming there is one, is low due to halting study designs. The hypothesis that there is an insulinotropic effect from milk that affects blood lipid levels can be neither confirmed nor rejected. Possible effects of milk need to be elucidated further.

References

1. Socialstyrelsen, Statistik - Hälsa och sjukdomar. 2008. Availible at: http://www.socialstyrelsen.se/NR/rdonlyres/89E19B44-AE9A-418F-8678-C2AEADC2F84E/11804/2008426_rev.pdf Accessed: 2009-04-29. (website)
2. FASS. Hjärt-kärlsjukdomar. 2008. Availible at: http://www.fass.se/LIF/lakarbok/artikel.jsp?articleID=5581 Accessed: 2009-04-29 (website)
3. Nilsson-Ehle P. Laurells Klinisk Kemi i praktisk medicin. Studentlitteratur AB 2003
4. Läkemedelsboken 2009-2010, Apoteket AB 2009
5. Ney, D M. Symposium: The Role of the Nutritional and Health Benefits in the Marketing of Dairy Products. Potential for Enhancing the Nutritional Properties of Milk Fat. Journal of Dairy Science 1991; 74: 4002-412
6. Keys A, Anderson J T and Grande F. Serum Cholesterol Response to Changes in the Diet. IV. Particular Saturated Fatty Acids in the Diet. Metabolism 1965 July; 14 (7)
7. Riksmaten 1997-1998. 1998. Availible at: http://www.slv.se/upload/dokument/rapporter/kostundersokningar/riksmat.pdf. Accessed: 2009-04-29 (website)
8. Nilsson M, Stenberg M, Frid A H, Holst J J and Björck I M E. Glycemia and insulinemia in healthy subjects after lactose-equivalent meals of milk and other food proteins: the role of plasma amino acids and incretins. American Journal of Clinical Nutrition 2004 Nov; 80 (5): 1246-1253
9. Hoyt G, Hickey M S and Cordain L. Dissociation of the glycaemic and insulinaemic responses to wholeand skimmed milk. British Journal of Nutrition 2005; 93: 175–177
10. Nilsson P M. Metabola syndromet : - bakgrund, mekanismer och behandling. Studentlitteratur AB 2006
11. Nordic Nutrition Recommendations 2004. Nordic Council of Ministers. Copenhagen 2004
12. Bosaeus I. Milk and cholesterol. Vår Föda 1991; 43: 98-101
13. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328;1490-doi:10.1136/bmj.328.7454.1490
14. Hepner G, Fried R, St Jeor S, Fusetti L, Morin R. Hypocholesterolemic effect of yogurt and milk. American Journal of Clinical Nutrition 1979; 32: 19-24
15. Hussi E, Miettinen T A, Ollus A. Lack of serum cholesterol-lowering effect of skimmed milk and butter milk under controlled conditions. Atherosclerosis 1981; 39 (2): 267-272
16. Rossouw J E, Burger E M, Van der Vyver P, Ferreira J J. The effect of skim milk, yoghurt, and full cream milk on human serum lipids. American Journal of Clinical Nutrition 1981 Mar; 34(3): 351-6
17. Thompson L U, Jenkins D J, Amer M A, Reichert R, Jenkins A, Kamulsky J. The effect of fermented and unfermented milks on serum cholesterol. American Journal of Clinical Nutrition 1982 Dec; 36 (6): 1106-11
18. Massey L K. Effect of changing milk and yogurt consumption on human nutrient intake and serum lipoproteins. Journal of Dairy Science 1984 Feb; 67(2): 255-62

19. Buonopane, G J, Kilara, A, Smith, J S, McCarthy, R D. Effect of skim milk supplementation on blood cholesterol concentration, blood pressure, and triglycerides in a free-living human population. Journal of the American College of Nutrition 1992; 11 (1): 56-67

20. Steinmetz, K A, Childs, M T, Stimson, C, Kushi, L H, McGovern, P G, Potter, J D, Yamanaka, W K. Effect of consumption of whole milk and skim milk on blood lipid profiles in healthy men. American Journal of Clinical Nutrition 1994; 59 (3): 612-618

21. American Heart Association. Rationale of the diet-heart statement of the American Heart Association. Circulation 1982; 65: 839A-54A

22. Barr S I, McCarron D A, Heaney R P, Dawson-Hughes B, Berga S L, Stern J S, Oparil S. Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. Journal of the American Dietetic Association 2000; 100 (7): 810-817

23. Kim J J and Kalkhoff R K. Changes in lipoprotein composition during the menstrual cycle. Metabolism 1979; 28: 663

Sammanfattande Evidensformulär Effektmått:

RCT utgår från ++++, kohortstudier utgår från ++. Sänk eller höj därefter graderingen utifrån studiekvalitet, överensstämmelse, överförbarhet, oprecisa data, risk för publikationsbias och effektstorlek.

Tillstånd:	
Åtgärd:	
Effektmått:	
Ingående studier: RCT ☐(++++) Kohortstudier ☐(++) Alla eller några av studierna sammanfattade i en systematisk översikt ☐ Antal studier: Antal pt:	+ 4 alt. +2
Studiedesign - Intern validitet (Randomiseringsförfarande, blindning, uppföljning, bortfall, intention-to-treat, vid kohortstudier – hantering av confounders) ☐Inga begränsningar ☐Vissa begränsningar (*men inte nog för nedgradering*[1]) ☐Allvarliga begränsningar (*minska ett steg*) ☐Mycket allvarliga begränsningar (*minska två steg*) Kommentera begränsningar eller grundvalen för nedgradering:	 ☐0 ☐ ? ☐-1 ☐-2
Överensstämmelse (Estimat av relativa effekten lika storlek och riktning mellan studierna? Överlappande konfidensintervall?) ☐Inga problem ☐Viss heterogenicitet (*men inte nog för nedgradering1*) ☐Bekymmersam heterogenicitet (*minska ett steg*) Kommentera brist på överensstämmelse eller grundvalen för nedgradering:	 ☐0 ☐ ? ☐-1

1

Studiepopulation – extern validitet(överförbarhet) Interventionen (effektmåttets relevans, relevans av jämförelsemetod, sjukvårdsmiljö, adekvat uppföljningstid)	
☐ Ingen osäkerhet	☐ 0
☐ Viss osäkerhet (*men inte nog för nedgradering1*)	☐ ?
☐ Osäkerhet (*minska ett steg*)	☐ -1
☐ Påtaglig osäkerhet (*minska två steg*)	☐ -2
Kommentera viss osäkerhet eller grundvalen för nedgradering:	
Oprecisa data (Få händelser, vida konfidensintervall som infattar möjlig ogynnsam effekt) - kohort	
☐ Inga problem	☐ 0
☐ Vissa problem med precision (*men inte nog för nedgradering1*)	☐ ?
☐ Oprecisa data (*minska ett steg*)	☐ -1
Kommentera viss osäkerhet eller grundvalen för nedgradering:	
Ösäkert underlag (Få och små studier från samma forskargrupp eller företag som alla visar samma sak)	
☐ Inga problem	
☐ Vissa problem (men inte nog för nedgradering1)	☐ 0
☐ Klar risk för publikationsbias (*minska ett steg*)	☐ ?
Kommentera grundvalen för nedgradering	☐ -1
Effektstorlek Vid stor effekt eller mycket stor effekt kan man uppgradera	

evidensstyrkan (Kohort) ☐ Ej relevant ☐ Stor effekt (RR<0,5 eller >2) (öka ett steg) ☐ Mycket stor effekt (RR<0,2 eller >5) (öka två steg) Kommentera grundvalen för uppgradering	☐0 ☐+1 ☐+2
Kommentera andra viktiga aspekter som ska beaktas vid kategorisering av evidensstyrka/bedömning av vetenskapligt underlag, t.ex. stark dos-respons, allt-eller-inget-effekter, confounders som maskerar del av effekt kan uppgradera evidensstyrkan. (kohort)	☐+1
Räcker summan av smärre brister under flera punkter till en nedgradering med ett helt steg? (beräkna antal ? i ovanstående frågor) ☐ Ja ☐Nej	 ☐-1 ☐0
Evidensstyrka ☐ Hög (++++) ☐ Måttlig (+++) ☐ Låg (++) ☐ Mycket låg (+) (= saknas vetenskapligt underlag)	

Dietistprogrammet
Sahlgrenska akademin vid
Göteborgs universitet

Gransknings- och dataextraktionsmall RCT

Författare: **Publikationsår** :

Studiedesign (*intern validitet)*

Randomisering ☐Adekvat ☐Kan ej värderas ☐Ej acceptabel pga…….....

Blindning ☐Patienten ☐Behandlaren ☐Utvärderaren ☐Ej acceptabel pga……..

Uppföljning under hur lång tid? …… veckor/månader/år

Bortfall % ☐Lika i alla grupper ☐Förklarat ☐Ej acceptabelt pga ……

Analys enligt intention to treat? ☐Ja ☐Nej ☐Framgår inte

Följsamhet till interventionen (adherence): % ☐ Ej angiven

Multicenter ☐Ja ☐ Nej Antal länder

Powerberäkning ☐Ja ☐ Nej

Studiepopulationen *(extern validitet)*

Ålder (medelålder):

Andel män/kvinnor:

Inklusionskriterier:

Exklusionskriterier:

Samtidig annan sjukdom/symptom:

Genomsnittlig duration av ev annan sjukdom

Land:

Sjukvårdsmiljö: ☐Primärvård☐Sjukhus, polikliniskt ☐Sjukhus, inneliggande

☐Ej angiven

Övriga karakteristika som är relevanta för studiens generaliserbarhet

Interventionen

Åtgärd/behandling i interventionsgruppen/grupperna (beskriv antal i varje grupp, doser, intensitet och duration)

……

……

……

Åtgärd/behandling i kontrollgruppen (beskriv antal, doser, intensitet och duration)

……

……

……

Effektmått

(Ringa in primärt e-mått)

Effektmått	**Mätmetod/utvärderingsmetod**	**Mätmetodens validitet** (bra/mindre bra/ ej acceptabelt/oklart)

Tabellering av resultat och precision

Effektmått	**Totalt antal patienter**	**Intervention** % eller medelvärde	**Kontroll** % eller medelvärde	**Absolut effekt** (Riskdifferens eller skillnad i medelvärden)	**Relativ effekt** (RR/OR)	**Mått på precision** (konfidensintervall, p-värde)

Kommentarer:

……

……

Sammanfattande värdering

……

……

……