OF COWS AND MEN: REVIEWING THE LINK BETWEEN MILK FAT AND HUMAN HEALTH

J.E. Rico[1] and D.E. Rico[2,3]
[1]Department of Animal Science, Cornell University
[2]CRSAD; [3]Department of Animal Science, Université Laval

INTRODUCTION

Milk is a unique, nutrient-dense, food. Key to early development of mammals, milk constitutes a major source of energy, high-quality protein, and vitamins and minerals such as vitamin D, calcium, and potassium (Smilowitz et al., 2005; Gaucheron, 2005). Beyond its key role in neonatal nutrition, milk and milk-derived products are also major sources of nutrients for adults. The ability of humans to carry on drinking milk through adulthood has developed gradually over the past eight millennia, in association with agriculture and dairying (Curry., 2013), and it is due to the persistence of the enzyme lactase past early childhood. The rise of distinct genetic mutations for lactase persistence developed in at least four different geographic regions on the planet (i.e., lactase hotspots), and, arguably, provided a major selective advantage (Bersaglieri, et al., 2004). Today, one-third of humans produce lactase during adulthood, with prevalence being greater in places like northern Europe, where over 90% of people can drink milk, but also in West Africa, the middle east, and south Asia (Curry., 2013; Liebert et al., 2017).

Despite the arguably obvious benefits that milk can provide to human populations as a source of nutrients, its place as a component of a healthy diet has been questioned. Indeed, over the past five decades, changes in consumer perception, dietary guidelines, public health messages, and policy, have all resulted in a shift in the patterns of consumption of milk and dairy products, particularly those of higher fat content. The start of these changes can be traced to the emergence of the “diet-heart hypothesis” in the 1950’s. Based on limited epidemiological data, its fundamental premise was that fat consumption could cause cardiovascular disease (**CVD**) in humans. In spite of being criticized as “invalid” and being based on a “tenuous association” from the onset (Yerushalmy and Hilleboe, 1957), the diet-heart hypothesis became a central piece of dietary advice in the following decades, in particular, to reduce CVD risk. A generalized “fear of fats” has spread since then and shaped consumer’s choices, who nowadays tend to look for reduced-fat foods as healthier alternatives to full-fat options, in hopes of reducing intake of fat and ‘calories’, and the risk of heart problems and obesity. Simultaneously, milk avoidance has become more prevalent (Figure 1), and new beverages of plant origin with low contents of saturated fats have become available, replacing cow’s milk in the diet (e.g., the so –called soy and almond milks). In contrast to current perceptions and dietary advice, an important body of literature has emerged over the past decade that challenges the contemporary views associating saturated animal fat consumption to human disease. Such studies suggest that dairy in general, as well as full-fat dairy, may decrease the risk for CVD. Furthermore, recent studies suggest that full fat dairy may actually protect from obesity and associated chronic diseases. This review

will summarize available evidence from recent meta-analyses, and observational and randomized controlled trials (**RCTs**), on the effects of dairy consumption on human health. The public health role of dairy products in relation to their potential to prevent or ameliorate the onset of chronic diseases will be discussed.

FAT CONSUMPTION AND HUMAN DISEASE

The Diet-heart Hypothesis - Background and Classic Studies

The now prevailing concept that saturated fats of animal origin are detrimental to human health can be traced to some suggestive pieces of evidence originated in the 20th century. First, the ground-breaking studies of Ignatowski in 1908 and Anichkov in 1913 demonstrated the ability of animal fats and, specifically, cholesterol, to cause atherosclerotic lesions, raise plasma cholesterol, and cause death in rabbit models of atherosclerosis (Konstantinov et al., 2006). Second, during the 1950's, Ancel Keys produced epidemiological data that seemed to identify dietary fat as a major cause of heart disease. In two commonly known studies, Keys and collaborators showed some seemingly strong associations between national death rates for middle-aged men from arteriosclerotic and degenerative heart disease and the proportion of fat-calories available in their national diets (Keys, 1953; Keys et al., 1966). His data relating availability of energy from fat and cardiovascular-related death led him to conclude that "dietary fat somehow is associated with cardiac disease mortality, at least in middle age". These studies propelled the extensively known diet-heart hypothesis that related dietary factors to the incidence of cardiovascular disorders. The validity of this hypothesis was quickly challenged by Yerushalmy and Hilleboe (1957), and its acceptance has remained far from unanimous ever since it was first proposed. In their methodological note, the authors attempted to evaluate whether the proposed hypothesis could actually reflect "known or ascertainable facts" which may allow for the generalization of this premise. The authors pointed at several limitations, including 1) small sample size (i.e., only 6 countries were used in Key's original study); 2) the possible effects of unaccounted confounders (e.g., underreporting in countries with lower economic status who cannot afford meat and dairy); 3) the fact that no actual data on fat consumption was used (i.e., availability was used); 4) the lack of specificity of the relationship (i.e., protein consumption also related to death); 5) variation in deaths from cardiac disease are largely variable across countries at any given fat availability category. Some interesting points emerging from their methodological analysis include: first, the strength of the association is greatly reduced when more countries are included (n= 22); second, the relationship is not specific to fat; third, "almost no association" was found when correlating fat or protein with all causes of death. This last point merits attention because CVD is the leading cause of death in industrial countries, and consequently, the relationship in Keys' studies would be expected to also hold for all-cause mortality. More recently, others (Willet, 2012) have pointed out that the countries chosen by Keys to represent low fat intake and low incidence of CVD were in fact less industrialized and showed differences in smoking habits, physical activity and obesity, thus complicating the generalization of the diet-heart hypothesis.

Dietary Lipids and CVD Risk

The importance of cholesterol in the development of CVD in humans was first suggested by data extracted from the Framingham study, which enrolled 5127 men and women aged 30–59 years in Massachusetts, starting between 1948 and 1950. Following six years of longitudinal evaluation, cholesterol was identified as one of three risk factors for CVD (Kannel et al., 1961)[1]. Several other studies between the 1950's and 1980's found positive associations between serum (total) cholesterol and risk of CVD. With the advent of techniques to identify and measure circulating lipoproteins, it was further shown that cholesterol contained in very low-density lipoproteins (**VLDL-C**), as well as low-density lipoproteins (**LDL-C**; i.e., 'bad cholesterol'), correlates positively with CVD risk, while that found in high density lipoproteins (**HDL-C**; i.e., 'good cholesterol), correlated negatively (see review by Parodi, 2009). In fact, LDL-C became the lead marker for atherogenicity and CVD risk, and thus, the main target and factor guiding CVD treatments in the last few decades (Stone et al., 2014). However, the role of LDL-C recently has been put into question as it is considered a very poor predictor of CVD (Sachdeva et al., 2009; Ravnskov et al., 2018). On the other hand, HDL-C (an indicator of cholesterol efflux) levels are used as a marker of reduced CVD risk (Rohatgi et al., 2014; Monette et al., 2016), particularly when used as a ratio of total cholesterol to HDL-C (Castelli, 1988). In addition, increased triglyceride to HDL-C ratio is a more powerful predictor of coronary heart disease (Luz et al., 2008).

While much of the focus has been historically placed on cholesterol, other factors seem to be important to predict CVD risk. Some of these include obesity, serum triglycerides, inactivity, hypertension, cigarette smoking and diabetes. Results from the Framingham cohort illustrate the importance of these cofactors, as, for example, accounting for glucose intolerance, high systolic blood pressure, smoking, and left ventricular hypertrophy increased CVD risk to 60.2, compared to only 3.9 when cholesterol alone was used (Kannel et al., 1979).

Saturated Fats and Blood Lipids

The ability of saturated fatty acids (**SFA**) to raise blood LDL-C is consistent across the literature, and it is well documented (Micha and Mozaffarian, 2008). Interest in this relationship stems from hypothesis that LDL particles may increase cholesterol accumulation in arterial walls, facilitating the formation of atheromatous plaque, and therefore increasing CVD risk (Kruth et al., 2001). Consequently, efforts have been made to determine the atherogenic potential of individual SFA as a marker of CVD. For example, Ulbricht and Southgate (1991) proposed the atherogenic index, which is calculated by dividing the sum the SFA lauric (12:0), myristic (14:0) and palmitic (16:0), by the sum of omega 3 and 6, 18:1c9, and other monounsaturated fatty acids. Based on Hegsted's work (1965), each factor is multiplied by an empirical constant according to its

[1] Indeed, interest in cholesterol seemed justified, as atheromatous lesions are rich in free and esterified cholesterol, relative to normal arterial walls (Windaus, 1910). Moreover, cholesterol alone can cause atheromatous lesions in the vascular wall (Anitschkow and Chalatow, 1913).

capacity to raise or decrease cholesterol, using a value of 1 for all fatty acids and a value of 4 for 14:0. Because these presumably atherogenic fatty acids (12:0, 14:0, 16:0) represent 30-40% of cow's milk triglycerides (Jensen, 2002; O'Donnell-Megaro et al., 2011), some have concluded that dairy fat is a potential cholesterol-raising food, and, consequently, consumers have reduced the consumption of full-fat dairy (Wang and Li, 2008). Simultaneously, official advice has focused on reducing the consumption of fat and saturated fat specifically. The dietary fat guidelines introduced in 1977 (US) and 1983 (UK) (Harcombe et al., 2015) recommend to 1) reduce overall fat consumption to 30% of total energy intake and 2) reduce saturated fat consumption to 10% of total energy intake. It is important to note that, with these guidelines, the ability of SFA to raise blood HDL-C, and to reduce CVD risk, is implicitly ignored (Parodi, 2009). In fact, a meta-analysis of 60 controlled trials showed that SFA have no effect on the ratio of total cholesterol to HDL-C (lower is better) when SFA replace dietary carbohydrates (Mensink, et al., 2003). Furthermore, the allegedly "atherogenic" lauric acid reduces the ratio, mostly by increasing HDL-C. These observations challenge the notion that SFA are indeed atherogenic and that SFA sources like milk fat may have health-adverse effects.

The disconnect between the expected effects of SFA-containing foods on CVD risk markers and the actual outcomes is well exemplified by the work of Lefevre et al., 2005. In this double-blind, randomized cross-over study, the authors report the effects of milk fat on health markers in males aged 22-64. Dietary supply of fat and SFA were adjusted by substituting low fat or non-fat dairy products for their higher fat equivalents. Energy from milk fat was progressively reduced to achieve fat and SFA energy consumption equivalent to an average American diet (**AAD**; 37% fat and 14% SFA; above current recommendations), and two diets with reduced fat and SFA content (**Step I diet**, 28% fat and 8.8% SFA; **Step II diet**, 24% fat and 6.2% SFA). The last two diets met current recommendations for energy intake from fat and SFA (Table 1).

Table 1. Reductions in dairy fat consumption result in higher blood triglycerides and Total:HDL-Cholesterol (Lefevre et al., 2005)

Effect of diets on lipid and lipoprotein concentrations[1]

	AAD 14% SFA	Step I diet 8.8% SFA	Step II diet 6.2% SFA
Total Cholesterol, mmol/L	4.82±0.69	4.59±0.6[2]	4.39±0.66[2,3]
Triacylglycerol, mmol/L	1.06±0.65	1.20±0.76[2]	1.22±0.80[2]
LDL Cholesterol, mmol/L	3.25±0.58	3.03±0.56[2]	2.87±0.52[2,3]
HDL Cholesterol, mmol/L	1.07±0.23	0.99±0.22[2]	0.95±0.22[2,3]
Apolipoprotein A-I, g/L	1.23±0.14	1.17±0.13[2]	1.15±0.12[2,3]
Apolipoprotein B, g/L	0.97±0.19	0.93±0.20[2]	0.9±0.18[2,3]
Total:HDL cholesterol	4.7±1.08	4.84±1.18[2]	4.85±1.26[2]

[1] All values are mean ± SD; n = 86. AAD, average American diet.
[2] Significantly different from AAD, $P < 0.05$ (ANOVA with Bonferroni corrections).
[3] Significantly different from Step I diet, $P < 0.05$ (ANOVA with Bonferroni corrections).

As expected, the reduction of dairy SFA consumption resulted in reduced circulating LDL-C. However, reductions of similar magnitude were observed for HDL-C. Furthermore, low fat diets increased circulating triglycerides and the ratio of total cholesterol to HDL-C (**Total:HDL-C**; i.e., the atherogenic ratio), both proxies for increased CVD risk. In this way, elevations observed by reducing dairy fat intake cast some concerns about the efficacy of low-fat diets to reduce CVD risk. Arguably, increased CVD risk may actually result from following this type of low-fat approach. Although factors like adiposity and insulin resistance of subjects may have influenced the responses to low-fat diets in this study, it is evident that the effects of such diets on the commonly used biomarkers (e.g., LDL-C, HDL-C, Total:HDL-C, and triglycerides) were certainly not what many may expect in terms of alleviation of CVD risk. Moreover, the validity of CVD biomarkers like LDL-C has dwindled recently, and the role of lipoproteins on CVD has shifted focus into their size (i.e., small and dense LDL profile is worse), number (i.e. Apolipoprotein B as a marker of atherogenic particles), and oxidation propensity, rather than their cholesterol content (Krauss, 2005; Parodi, 2009). An example comes from the guidelines of the American Heart Association, who, based on a recent review of available data, reported being unable to find evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets. In this way, the “bad cholesterol” is no longer the main factor guiding treatment (Stone et al., 2014).

Even leaving CVD lipid biomarkers aside, under the diet-heart hypothesis, the effects of SFA on actual clinical outcomes should reflect harmful consequences on cardiovascular endpoints. Contrary to this expectation, a meta-analysis of prospective cohort studies that followed 347,747 subjects for 5 to 23 years found no association between saturated fat intake and CVD, both fatal and non-fatal (Siri-Tarino et al., 2010). Similarly, in a systematic review and meta-analysis of prospective cohort studies and RCTs (n = 78) with 649,812 participants, Chowdhury et al. (2014) reported no increase of relative risk of coronary outcomes associated with dietary or circulating SFA. Moreover, the authors reported an inverse association between circulating margaric acid (17:0, a marker of dairy fat intake) and coronary disease. Taken together, available evidence from prospective epidemiologic studies and RCT does not support guidelines encouraging reduced saturated fat consumption, particularly those from dairy. Whether this evidence can be considered sufficient to totally vindicate SFA and dairy, is still a matter for discussion; however, currently available data suggest the heavy focus on saturated fats may be not only unnecessary, but perhaps also detrimental. This is particularly true when considering that dairy fats may have been replaced with industrial *trans* fats of plant origin (e.g. margarines with high *trans* fat content), as well as refined sugars (i.e., fructose). Some trends exemplifying these dietary substitutions can be seen in Figure 1. Full fat milk has been partially substituted with lower-fat versions, while soft drinks consumption and fructose has risen in linearly. Importantly, there are cogent reasons to believe that the simultaneous reduction in consumption of some dairy products and the increase industrial *trans* fats and sugars could be detrimental. For example, non-ruminant (i.e., industrial) *trans* fats are nowadays recognized as harmful (Micha and Mozaffarian, 2008) and they relate strongly to heart disease and all-cause mortality (Oomen et al., 2001; de Souza et al., 2015). Similarly, a growing body of evidence indicates that most US adults currently consume excess added sugar (a source of fructose), and this is significantly associated

with obesity, metabolic syndrome, and CVD mortality (Johnson et al., 2009; Lustig et al., 2010; Yang et al., 2014). In fact, the American Heart Association has recommended the reduction of dietary sugar intake by more than half (Johnson et al., 2009).

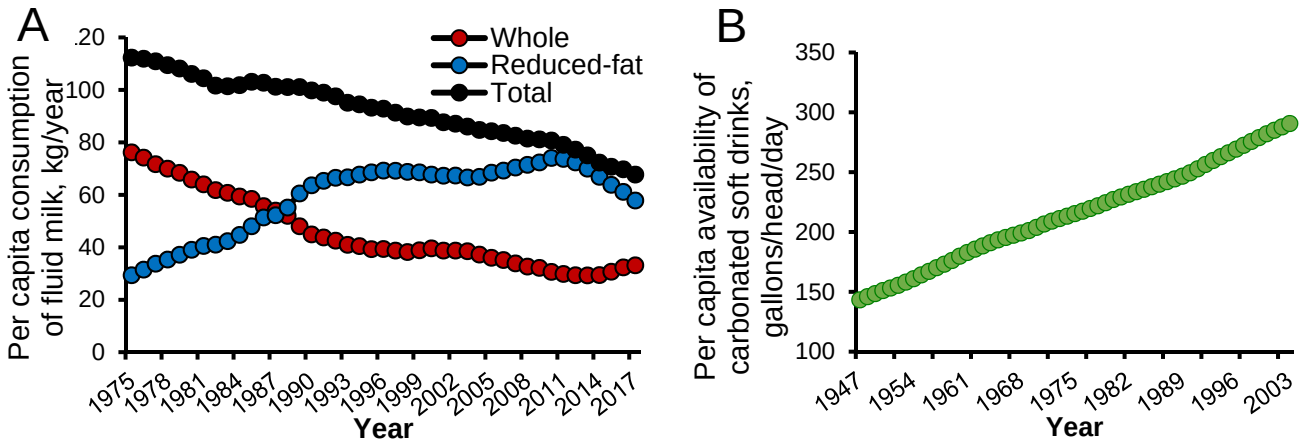

Figure 1. (A) Trends of consumption of fluid milk as reduced-fat milks and whole milk from 1975 to 2017 in the U.S. (B) Per capita availability (gallons/head/day) of carbonated soft drinks, 1947 - 2003 Source: USDA, Economic Research Service. 2012; 2018.

DAIRY CONSUMPTION AND HUMAN HEALTH OUTCOMES

A Note on the Assessment of Evidence

Evidence for claims related to lipid intake and human health come from a range of studies with varying degrees of causal strength, going from observational studies to controlled randomized clinical trials. Young and Karr (2011) give some perspective on the frequency at which observational claims fail to replicate, at an alarming rate of 80%. Further, in about 10% of the cases, when the claims from observational studies were tested in clinical trials they moved significantly in the opposite direction (Young and Karr; 2011). These authors suggested that ‘‘any claim coming from an observational study is most likely to be wrong – wrong in the sense that it will not replicate if tested rigorously’’. Therefore, assessing the observational evidence that relates dietary intakes to common disease outcomes is, at the very least, problematic (Prentice, 2014). For instance, the validity of observational studies can be compromised by the necessary reliance placed on self-reported food intakes and can further be complicated by the effects of confounders, such as lifestyle factors that may impact the association. This highlights some of the problems with claims originated from ecological studies, such as the diet-heart hypothesis, which now seems to lose validity in the face of stronger pieces of evidence, such as RCTs and prospective cohort studies, which contradict its original presuppositions (e.g., Micha and Mozaffarian, 2008; Ramsden et al., 2016). While bearing these limitations in mind, the interpretation of observational studies relating dairy intake and health outcomes can be in many instances a useful starting point for

investigation and validation. Regardless, causation may only be derived from properly controlled experimentation.

Obesity and Type 2 Diabetes

One arguably important reason for the current trends of dairy fat avoidance (Figure 1) is related to the interest in reducing excess energy intake. The common presumption is that dairy fat can be stored as body fat and thus contribute to weight gain, obesity, and cardiometabolic risk. This has driven dietary guidelines to recommend the consumption of low-fat dairy (Jensen et al., 2014). In contrast to guidelines and prevailing public sentiment, available evidence indicates dairy fat consumption is not related with the risk of weight gain. The comprehensive review of Kratz et al. (2013), which used a combination of observational and controlled studies, indicates that dairy fat consumption, both recorded or assessed via odd-chain fatty acid content in blood (e.g., 15:0 and 17:0), was inversely related with obesity risk. Similar findings were reported in a cross-sectional evaluation of full-fat milk consumption in three-year-old children (Beck et al., 2017). The multivariate analysis included potential demographic and nutritional confounders. The authors reported reduced odds for severe obesity in association with higher milk fat consumption, suggesting a protective effect of dairy fat against obesity in three-year-olds. Similarly, in a prospective cohort study of 18,438 healthy middle-aged women followed during 11 years and belonging to the Women's Health Study, greater consumption of total dairy products reduced the risk of becoming overweight or obese. Furthermore, the lowest risk was observed at the highest quintile of high-fat dairy product intake (Rautiainen et al., 2016). Finally, in a meta-analysis of 29 RCTs, Chen et al. (2012) reported dairy consumption does not increase body weight gain or body fat gain. Moreover, dairy consumption results in modest beneficial effects on weight loss in short-term and energy-restricted RCTs.

Type 2 diabetes (**T2D**) is rapidly rising worldwide, paralleling the epidemic increase in obesity. Because of its high content of calcium, magnesium, vitamin D, and whey proteins, which could reduce insulin resistance, dairy products could be hypothesized to protect against T2D (Rice et al., 2011). The meta-analysis of Aune et al. (2013) evaluated the association between intake of dairy products and the risk of T2D from prospective cohort and nested case-control studies (n=17). Non-linear, inverse associations were found between the risk of T2D and intakes of dairy products, low-fat dairy, yogurt, and cheese, the latter being the highest in fat content. The risk responses to dairy intake were dose-dependent, and flattened at higher intakes. Interestingly, high fat dairy did not alter the T2D risk in this study, although a meta-analysis focused specifically on butter consumption (Pimpin et al., 2016; 11 country-specific cohorts and 201,628 participants) reported butter intake was associated with a reduction of T2D risk. This discrepancy may suggest that the effects of dairy fat may be food-specific (e.g. cheese different from butter), a concept that merits further investigation. Other recent meta-analyses add support to the protective effects of dairy consumption against T2D (Forouhi et al., 2014; de Souza et al., 2015; Yakoob et al., 2016). For example, the prospective associations between circulating fatty acids in phospholipids and T2D were reported in individuals from the EPIC-InterAct case-cohort study (17,928 T2D subjects and 16,835 participants in a

random subcohort; Forouhi et al., 2014). By design, this study combines the temporal sequence and power advantages of a larger prospective cohort, with the measurement efficiency of a case-control. Forouhi et al., 2014 reported reduced hazard ratios for incident T2D in association with the odd chain SFA 15:0 and 17:0, both of which are mostly derived from dairy products. Similarly, using two prospective cohorts with 3333 adults aged 30 to 75 years, free of T2D at baseline, and followed during 15 years, Yakoob et al. (2016) found that individuals at the highest quartile of plasma 15:0, 17:0, and *t*-16:1n-7 had reduced risk of incident diabetes mellitus (-44%, -43%, and -53%, respectively; Figure 2). This last finding is of particular interest given that other studies have showed that circulating *trans*-palmitoleic acid (*t*-16:1n-7) is associated with lower insulin resistance, atherogenic dyslipidemia, and incident diabetes (Mozaffarian et al., 2010; de Souza et al., 2015). Importantly, whole-fat dairy consumption is most associated with elevated plasma concentrations of *trans*-palmitoleic acid (Mozaffarian et al., 2010). Whether the apparently beneficial effects of dairy on T2D risk are mediated by *trans*-palmitoleic acid or other components of dairy, remains to be experimentally elucidated; regardless, this possibility constitutes an exciting new direction for fatty acid research.

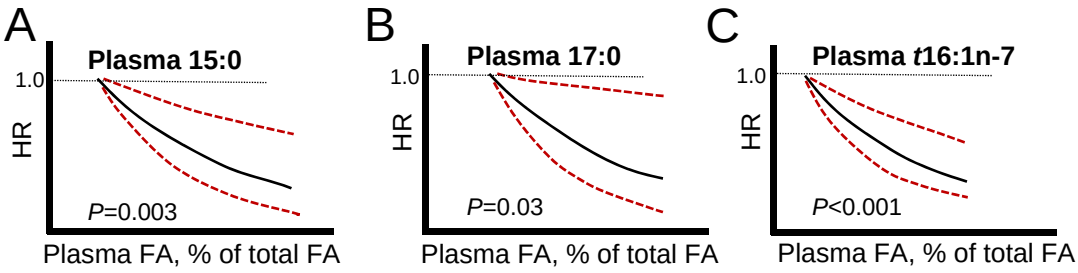

Figure 2. Circulating biomarkers of dairy fat intake and risk of incident diabetes mellitus in two large prospective cohorts using 3,333 adults in a 15-year follow-up (Adapted from Yakoob et al., 2016). Solid-black and dashed-red lines represent hazard ratios (HR) and their 95% confidence intervals, respectively, for plasma A)15:0, B)17:0, and C) *t*-16:1n-7.

Metabolic Syndrome

Metabolic syndrome (**MetS**) consists of a cluster of cardiovascular risk factors that include central obesity, hyperglycemia, hypertriglyceridemia, low HDL-C, and hypertension (Alberti et al., 2009). Moreover, MetS is closely associated with CVD risk, T2D, all-cause mortality and cancer (Saely et al., 2007; Wu et al., 2010; Esposito et al., 2012). Despite the recognition of the potential of dairy products to prevent or alleviate CVD, T2D and blood pressure in adults (e.g., 2010 Dietary guidelines for Americans; USDA/USDHHS, 2010), data on the relationship between dairy consumption and MetS is very limited. Chen et al. (2015) evaluated currently available data from cross-sectional/case control studies (n=16) and prospective cohort studies (n=7) in two different meta-analyses. Comparing high vs. low dairy products intake, both meta-analyses showed a reduction in MetS risk with high dairy consumption, an observation that was maintained when the studies were evaluated by stratified subgroups (e.g. geographic region, sex, type of dairy, and follow-up duration). Finally, a dose response analysis of

prospective cohorts in the same study showed an inverse relation between MetS risk and dairy consumption (Chen et al., 2015). Interestingly, the reduction in risk became evident when dairy intake was higher than 2 servings per day, and behaved linearly thereafter. This would suggest a minimum amount of dairy may be needed to impact MetS risk in a beneficial manner.

CVD Risk and CVD Mortality

As discussed previously, the relationship between SFA consumption and CVD is not straightforward, and it was historically derived from the diet-heart hypothesis, with two important premises: 1) SFA can influence circulating cholesterol (i.e., increase LDL-C), and 2) cholesterol is a risk factor for CVD. The resulting assumption was, therefore, that SFA consumption can cause CVD. Given the disconnect between SFA consumption and the anticipated clinical CVD outcomes (e.g., Siri Tarino et al., 2010; Chowdhury et al., 2014), the strength of the diet-heart hypothesis has been questioned. Considering that dairy products may have protective effects against obesity, T2D, and metabolic syndrome, it is important to elucidate whether this may also be true for CVD, which remains a major cause of death in the United States (Mozaffarian et al., 2015). When looking at the effects of dairy consumption on CVD risk factors, the most salient finding is that, contrary to expectations, reducing SFA intake from dairy increases CVD risk, as determined by commonly used markers (Lefevre et al., 2005; Table 1). This sobering observation seems to receive further support from other studies that report significant associations between milk-derived fatty acids and a more favorable LDL particle size distribution (i.e., reduction in small dense LDL particles; Sjogren et al., 2004). Furthermore, some SFA found in milk fat, such as lauric acid, are actually associated with a reduction of CVD risk (Micha and Mozaffarian., 2010). Importantly, these pieces of evidence align with the solid, general observation, that SFA are neutral or even beneficial in terms of CVD risk.

Focusing on evidence from prospective data, Elwood et al., (2008) conducted a meta-analysis of 15 prospective cohort studies reporting the association between milk and dairy consumption and the incidence of vascular diseases in the UK. The relative risk (RR) of stroke and/or heart disease was significantly reduced in subjects with high milk or dairy consumption (RR =0.84 and 0.79, respectively), compared with the risk in those with low consumption. These findings highlight once more, the disconnect between the hypothesized effects of SFA-containing foods like dairy, and the actual clinical outcomes of interest. Similarly, a systematic review of the available literature indicates that most studies do not support the expected effects of dairy fat on CVD, and that discrepancies may be associated to country-specific effects (Kratz et al., 2012). Specifically, the Nurses' Health study (from the US) found a consistent positive association between dairy fat intake and CVD, while 11 other studies across Europe, Costa Rica, and Australia, showed either no association or an inverse relationship between CVD and dairy fat intake. Only one of these 11 studies reported a discrepancy, as it found an inverse association in men, but a positive one in women (Kratz et al., 2012). The authors suggested that residual confounding from lifestyle factors associated with dairy intake, as well as differences in food sources of dairy fat, may help explain the discrepancy between US and non-US data.

Relevant to this point, the recently published results from the Prospective Urban Rural Epidemiology (**PURE**) study evaluated the effects of dairy consumption on death and major CVD events across 21 countries and 5 continents in an 9-year follow-up (Dehghan et al., 2018). Dietary intakes of dairy products for 136,384 individuals were recorded using country-specific validated food frequency questionnaires. Dairy foods evaluated included milk, yoghurt, and cheese, and these were grouped into whole-fat and low-fat dairy. Dairy intake above 2 servings per day reduced the risk of total mortality, CVD mortality, major CVD, and stroke, relative to no intake. Similarly, whole-fat dairy (> 2 servings per day) was inversely associated with total mortality and major CVD. Interestingly, the CVD response to whole-fat dairy appeared to be dose-responsive, as it increased progressively from <0.5 to 0.5-1, 1-2, and >2 servings per day. Cheese consumption (>1 serving per day) was associated with reduced mortality and major CVD, while the effect of butter was neutral (i.e., no increase in risk). The PURE study suggests that dairy intake, especially whole-fat dairy, might be beneficial for preventing deaths and major cardiovascular diseases. Moreover, there seems to be no disadvantage associated with the consumption of full-fat dairy, compared with the low-fat counterparts. The authors conclude that consumption of dairy products should not be discouraged and perhaps should even be encouraged, particularly in low-income and middle-income countries where dairy consumption is low.

The mechanistic modes of action by which milk and dairy products may be protective against CVD and other health outcomes is likely complex and still requires investigation. It is important to bear in mind that bovine milk contains an outstanding number of bioactive components (Park, 2009), which may interact additively, synergistically, or antagonistically. The heavy focus on single nutrients during the past decades (e.g., saturated fats should be avoided) has proven narrow in scope and of limited ability to predict health outcomes. As proposed by others (Mozaffarian, 2014), food-based guidelines that reduce confusion for consumers and are based on prospective evidence for effects on clinical endpoints are needed.

CONCLUSION

We may be in the midst of a paradigm shift in human nutrition. The revaluation of the validity of classic literature and the emerging plethora of evidence over the past decade, strongly contradict the long-held idea that dietary saturated fats cause adverse effects on health. Moreover, as shown in this review, current evidence indicates that dairy products, including full-fat dairy, may exert protective effects on metabolic health, reducing the incidence of obesity, T2D, MetS, CVD, and mortality. In light of this evidence, a general call to revise the guidelines on dairy consumption seems strongly justified and necessary, particularly as dairy products may help combat the spread of chronic diseases. Moreover, the historic focus on individual nutrients (e.g., fat, calories) has proven limited in terms of predicting clinical outcomes. In this sense, a whole-food approach to studying the effects of the ensemble of nutrients contained in dairy foods on human health outcomes seems warranted. Lastly, policy changes should be guided by a more nuanced interpretation of observational studies, and reflect the value of repeatable, randomized controlled studies, as the latter may provide insights on causality and the role of dairy on public health.

ACKNOWLEDGEMENTS

The authors thank Magdalena Masello, at Cornell University, for careful reading of this manuscript and helpful comments.

REFERENCES

Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.C., James, W.P.T., Loria, C.M. and S.C. Smith Jr. 2009. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 120:1640-1645.

Anitschkow N. und S. Chalatow. 1913. Ueber experimentelle Cholester-insteatose und ihre Bedeutung fuer die Entstehung einiger pathologischer Prozesse. Zentrbl. Allg. Pathol. Pathol. Anat. 24:1–9.

Aune, D., Norat, T., Romundstad, P. and L.J. Vatten. 2013. Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies–. Am. J. Clin. Nutr 98:1066-1083.

Beck, A.L., Heyman, M., Chao, C. and J. Wojcicki. 2017. Full fat milk consumption protects against severe childhood obesity in Latinos. Prev. Med. Rep. 8:1-5.

Bersaglieri, T., Sabeti, P.C., Patterson, N., Vanderploeg, T., Schaffner, S.F., Drake, J.A., Rhodes, M., Reich, D.E. and J.N. Hirschhorn. 2004. Genetic signatures of strong recent positive selection at the lactase gene. Am. J. Hum. Genet. 74:1111-1120.

Castelli, W.P. 1988. Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. Can. J. Cardiol. 4:5A-10A.

Chen, G.C., Szeto, I.M., Chen, L.H., Han, S.F., Li, Y.J., Van Hekezen, R. and L.Q. Qin. 2015. Dairy products consumption and metabolic syndrome in adults: systematic review and meta-analysis of observational studies. Sci. Rep. 5:14606.

Chowdhury, R., Warnakula, S., Kunutsor, S., Crowe, F., Ward, H.A., Johnson, L., Franco, O.H., Butterworth, A.S., Forouhi, N.G., Thompson, S.G. and K.T. Khaw. 2014. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann. Intern. Med. 160:398-406.

Curry, A., 2013. The milk revolution. Nature 500:20.

Dehghan, M., Mente, A., Rangarajan, S., Sheridan, P., Mohan, V., Iqbal, R., Gupta, R., Lear, S., Wentzel-Viljoen, E., Avezum, A. and P. Lopez-Jaramillo. 2018. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. The Lancet. https://doi.org/10.1016/S0140-6736(18)31812-9

De Souza, R.J., Mente, A., Maroleanu, A., Cozma, A.I., Ha, V., Kishibe, T., Uleryk, E., Budylowski, P., Schünemann, H., Beyene, J. and S.S. Anand. 2015. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. Bmj. 351p.h3978.

Elwood, P.C., Givens, D.I., Beswick, A.D., Fehily, A.M., Pickering, J.E. and J. Gallacher. 2008. The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases, diabetes and cancer. J. Am. Coll. Nutr. 27:723S-734S.

Esposito, K., Chiodini, P., Colao, A., Lenzi, A. and D. Giugliano. 2012. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 35:2402–2411

Forouhi, N.G., Koulman, A., Sharp, S.J., Imamura, F., Kröger, J., Schulze, M.B., Crowe, F.L., Huerta, J.M., Guevara, M., Beulens, J.W. and G.J. van Woudenbergh. 2014. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. Lancet Diabetes Endocrinol. 2:810-818.

Gaucheron, F. 2005. The minerals of milk. Reprod. Nutr. Dev. 45: 473-483.

Harcombe, Z., Baker, J.S., Cooper, S.M., Davies, B., Sculthorpe, N., DiNicolantonio, J.J. and f. Grace. 2015. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open heart 2:p.e000196.

Hegsted, D.M., R. B. McGandy, M. L. Myers, and F.J. Stare. 1965. Quantitative effects of dietary fat on serum cholesterol in man. Am. J. Clin. Nutr. 17:281-295.

Jensen, M.D., Ryan, D.H., Apovian, C.M., Ard, J.D., Comuzzie, A.G., Donato, K.A., Hu, F.B., Hubbard, V.S., Jakicic, J.M., Kushner, R.F. and C.M. Loria. 2014. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J. Am. Coll. Cardiol. 63:2985-3023.

Jensen, R. G. The composition of bovine milk lipids: January 1995 to December 2000. 2002. J. Dairy Sci., 85:295–350.

Johnson, R.K., Appel, L.J., Brands, M., Howard, B.V., Lefevre, M., Lustig, R.H., Sacks, F., Steffen, L.M. and J. Wylie-Rosett. 2009. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation 120:1011-1020.

Kannel, W.B., Castelli, W.P. and Gordon, T., 1979. Cholesterol in the prediction of atherosclerotic disease: new perspectives based on the Framingham Study. Ann. Intern. Med. 90:85-91.

Kannel, W.B., Dawber, T.R., Kagan, A., Revotskie, N. and Stokes, J., 1961. Factors of risk in the development of coronary heart disease—six-year follow-up experience: the Framingham Study. Ann. Intern. Med. 55:33-50.

Keys, A., Aravanis, C., Blackburn, H.W., Van Buchem, F.S., Buzina, R., Djordjevic, B.D., Dontas, A.S., Fidanza, F., Karvonen, M.J., Kimura, N. and D. Lekos. 1966. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med. Scand. Suppl. 460:1–392.

Keys, A., 1953. Atherosclerosis: a problem in newer public health. Atherosclerosis 1:19.

Konstantinov, I.E., Mejevoi, N. and Anichkov, N.M., 2006. Nikolai N. Anichkov and his theory of atherosclerosis. Tex. Heart Inst. J. 33:417.

Krauss, R.M., 2005. Dietary and genetic probes of atherogenic dyslipidemia. Arterioscler. Thromb. Vasc. Biol. 25:2265-2272.

Kruth, H. S. 2001. Lipoprotein cholesterol and atherosclerosis. Curr. Mol. Med. 1:633-653.

Lefevre, M., Champagne, C.M., Tulley, R.T., Rood, J.C. and M.M. Most. 2005. Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol–. Am. J. Clin. Nut. 82:957-963.

Liebert, A., López, S., Jones, B.L., Montalva, N., Gerbault, P., Lau, W., Thomas, M.G., Bradman, N., Maniatis, N. and D.M. Swallow. 2017. World-wide distributions of lactase persistence alleles and the complex effects of recombination and selection. Hum. Genet. 136:1445-1453.

Lustig, R. H. 2010. Fructose: Metabolic, hedonic, and societal parallels with ethanol. J. Am. Diet. Assoc.110:1307-1321.

Luz, P. L. D., Favarato, D., Faria-Neto Junior, J. R., Lemos, P., and A.C.P. Chagas. 2008. High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. Clinics 63:427-432.

Mensink, R.P., Zock, P.L., Kester, A.D. and M.B. Katan. 2003. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am. J. Clin. Nut. 77:1146-1155.

Micha, R. and D. Mozaffarian. 2008. Trans fatty acids: effects on cardiometabolic health and implications for policy. Prostaglandins Leukot. Essent. Fatty Acids 79:147-152.

Monette, J.S., Hutchins, P.M., Ronsein, G.E., Wimberger, J., Irwin, A.D., Tang, C., Sara, J.D., Shao, B., Vaisar, T., Lerman, A. and J.W. Heinecke. 2016. Patients with coronary endothelial dysfunction have impaired cholesterol efflux capacity and reduced HDL particle concentration. Circ. Res. 119:83-90.

Mozaffarian, D., 2014. Saturated fatty acids and type 2 diabetes: more evidence to re-invent dietary guidelines. Lancet Diabetes Endocrinol. 2:770-772.

Mozaffarian, D., Cao, H., King, I.B., Lemaitre, R.N., Song, X., Siscovick, D.S. and G.S. Hotamisligil. 2010. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in US adults: a cohort study. Ann. Intern. Med. 153:790-799.

Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., Das, S.R., de Ferranti, S., Després, J.P., Fullerton, H.J. and V.J. Howard. 2015. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation CIR-0000000000000350.

Oomen, C.M., Ocké, M.C., Feskens, E.J., van Erp-Baart, M.A.J., Kok, F.J. and Kromhout, D., 2001. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. The Lancet 357:746-751.

Ordovas, J.M. 2005. Diet-heart hypothesis: will diversity bring reconciliation?. Am J Clin Nutr. 82(5):919-20.

O'Donnell-Megaro, A.M., Barbano, D.M. and Bauman, D.E., 2011. Survey of the fatty acid composition of retail milk in the United States including regional and seasonal variations. J. Dairy Sci. 94:59-65.

Park, Y.W. ed., 2009. *Bioactive components in milk and dairy products*. John Wiley & Sons.

Parodi, P.W., 2009. Has the association between saturated fatty acids, serum cholesterol and coronary heart disease been over emphasized?. Int. Dairy J. 19:345-361.

Pimpin, L., Wu, J.H., Haskelberg, H., Del Gobbo, L. and D. Mozaffarian. 2016. Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. PLoS One 11:p.e0158118.

Prentice, A.M., 2014. Dairy products in global public health–. Am. J. Clin. Nutr. 99:1212S-1216S.

Ramsden, C.E., Zamora, D., Majchrzak-Hong, S., Faurot, K.R., Broste, S.K., Frantz, R.P., Davis, J.M., Ringel, A., Suchindran, C.M. and J.R. Hibbeln. 2016. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). Bmj. 353:1246.

Rautiainen, S., Wang, L., Lee, I.M., Manson, J.E., Buring, J.E. and H.D. Sesso. 2016. Dairy consumption in association with weight change and risk of becoming overweight or obese in middle-aged and older women: a prospective cohort study–3. Am. J. Clin. Nutr. 103:979-988.

Rice, B.H., Cifelli, C.J., Pikosky, M.A. and G.D. Miller. 2011. Dairy components and risk factors for cardiometabolic syndrome: recent evidence and opportunities for future research. Adv. Nutr. 2:396-407.

Rohatgi, A., Khera, A., Berry, J.D., Givens, E.G., Ayers, C.R., Wedin, K.E., Neeland, I.J., Yuhanna, I.S., Rader, D.R., de Lemos, J.A. and P.W. Shaul. 2014. HDL cholesterol efflux capacity and incident cardiovascular events. N. Engl. J. Med. 371:2383-2393.

Sachdeva, A., Cannon, C.P., Deedwania, P.C., LaBresh, K.A., Smith Jr, S.C., Dai, D., Hernandez, A. and G.C. Fonarow. 2009. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am. Heart J. 157:111-117.

Saely, C. H., Rein, P. and H. Drexel. 2007. The metabolic syndrome and risk of cardiovascular disease and diabetes: experiences with the new diagnostic criteria from the International Diabetes Federation. Horm. Metab. Res. 39:642–650.

Smilowitz, J. T., Dillard, C. J., and J.B. German. 2005. Milk beyond essential nutrients: the metabolic food. Aust. J. Dairy Technol. 60:77.

Siri-Tarino, P.W., Sun, Q., Hu, F.B. and R.M. Krauss. 2010. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am. J. Clin. Nutr. 91:535-546.

Soedamah-Muthu, S.S., Ding, E.L., Al-Delaimy, W.K., Hu, F.B., Engberink, M.F., Willett, W.C. and J.M. Geleijnse. 2010. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies–. Am. J. Clin. Nutr. 93:158-171.

Stone, N.J., Robinson, J.G., Lichtenstein, A.H., Merz, C.N.B., Blum, C.B., Eckel, R.H., Goldberg, A.C., Gordon, D., Levy, D., Lloyd-Jones, D.M. and P. McBride. 2014. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am Coll. Cardiol. 63:2889-2934.

Ravnskov, U., de Lorgeril, M., Diamond, D.M., Hama, R., Hamazaki, T., Hammarskjöld, B., Hynes, N., Kendrick, M., Langsjoen, P.H., Mascitelli, L. and K.S. McCully. 2018.

LDL-C Does Not Cause Cardiovascular Disease: a comprehensive review of current literature. Expert. Rev. Clin. Pharmacol. [Epub ahead of print]. doi: 10.1080/17512433.2018.1519391.

Ulbricht, T.L.V. and D.A.T, Southgate. 1991. Coronary heart disease: seven dietary factors. The Lancet 338:985-992.

USDA, Economic Research Service. 2012. USDA/Economic Research Service estimate using data from the Census of Manufactures. Data last updated Feb. 1, 2012. http://www.ers.usda.gov/data-products/food-availability-(per-capita)-data-system.aspx.

USDA, Economic Research Service. 2018. “Fluid beverage milk sales by product.” https://www.ers.usda.gov/data-products/dairy-data/.

USDA/USDHHS. U.S. Department of Agriculture and U.S. Department of Health and Human Services. 2010. Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010. http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm

Wang, Y., and S. Li. 2008. Worldwide trends in dairy production and consumption and calcium intake: is promoting consumption of dairy products a sustainable solution for inadequate calcium intake?. Food Nutr. Bull. 29:172-185.

Willett, W.C. 2012. Dietary fats and coronary heart disease. J. Intern. Med. 272:13-24.

Windaus A. 1910. Ueber der Gehalt normaler und atheromatoser Aorten an Cholesterol und Cholesterinester. Zeitschrift. Physiol. Chemie. 67:174.

Wu, S. H., Liu, Z. and S.C. Ho. Metabolic syndrome and all-cause mortality: a meta-analysis of prospective cohort studies. Eur. J. Epidemiol. 25:375–384.

Yakoob, M.Y., Shi, P., Hu, F.B., Campos, H., Rexrode, K.M., Orav, E.J., Willett, W.C. and D. Mozaffarian. 2014. Circulating biomarkers of dairy fat and risk of incident stroke in US men and women in 2 large prospective cohorts–. Am. J. Clin. Nutr. 100: 1437-1447.

Yang, Q., Zhang, Z., Gregg, E.W., Flanders, W.D., Merritt, R. and F.B. Hu. 2014. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern. Med. 174:516-524.

Yerushalmy, J. and H.E. Hilleboe. 1957. Fat in the diet and mortality from heart disease; a methodologic note. N. Y. State J Med. 57:2343.

Young, S.S. and A. Karr. 2011. Deming, data and observational studies. Significance, 8:116-120.