Review: dairy foods, red meat and processed meat in the diet: implications for health at key life stages

Article

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Short title: Animal-derived foods and health at key life stages

Abstract

Social and health care provision have led to substantial increases in life expectancy. In the UK this has become higher than 80 years with an even greater proportional increase in those aged 85 years and over. The different life stages give rise to important nutritional challenges and recent reductions in milk consumption have led to sub-optimal intakes of calcium by teenage females in particular when bone growth is at its maximum and of iodine during pregnancy needed to ensure that supply/production of thyroid hormones to the foetus is adequate. Many young and premenopausal women have considerably sub-optimal intakes of iron which are likely to be associated with reduced consumption of red meat. A clear concern is the low intakes of calcium especially since a high proportion of the population is of sub-optimal vitamin D status. This may already have had serious consequences in terms of bone development which may not be apparent until later life, particularly in post-menopausal women. This review aims to examine the role of dairy foods and red meat at key life stages in terms of their ability to reduce or increase chronic disease risk. It is clear that milk and dairy foods are key sources of important nutrients such as calcium and iodine and the composition of some key nutrients, notably iodine can be influenced by the method of primary milk production, in particular the iodine intake of the dairy cow. Recent meta-analyses show no evidence of increased risk of cardiovascular diseases from high consumption of milk and dairy foods but increasing evidence of a reduction in the risk of type 2 diabetes associated with fermented dairy foods, yoghurt in particular. The recently updated reports from the World Cancer Research Fund International / American Institute for Cancer Research on the associations between dairy foods, red meat and processed meat and various cancers provide further confidence that total dairy products and milk, are associated with a reduced risk of colorectal cancer and high intakes of milk/dairy are not associated with increased risk of breast cancer. Earlier evidence of a significant increase in the risk of colorectal cancer from consumption of red and particularly processed meat has been reinforced by inclusion of more recent studies. It is essential that nutrition and health-related functionality of foods are included in evaluations of sustainable food production.

Key words: Milk, dairy products, red and processed meat, cardiometabolic diseases, cancer

Implications

Milk/dairy foods provide important nutrients that are of benefit to most people throughout life. Many young women consume too little calcium, magnesium and vitamin D and the risk of this to bone health may not be fully realised until they are in late middle age. There is good evidence that milk/dairy foods are not associated with an increase in the risk of cardiovascular disease and that fermented dairy foods are linked with reduced risk of type 2 diabetes, very important as the prevalence of this condition is increasing rapidly. More evidence points to the increased cancer risk associated with processed meat but this should be considered alongside other lifestyle-choice risks and the underlying risk so that absolute risk can be estimated.

Introduction

Over the last 200 years populations in most countries have had substantial improvements in health care which has given rise to increases in life expectancy. In the UK, life expectancy doubled over this period and is now higher than 80 years (Roser, 2017) and an even greater population growth rate has been seen among those aged 85 years and over. Ageing brings with it some important nutritional challenges such as sarcopenia, those related to reduced absorption of vitamin B_{12} and efficiency of vitamin D synthesis and associated health problems. For example, the frequency of osteoporotic fracture has increased in many countries and it has been estimated that the prevalence will double in the EU by 2035 (Hernlund *et al*., 2013). In middle and later life cardiovascular diseases (CVD) are still a major cause of death and morbidity in the EU and worldwide despite improved prevention and treatment programmes (Wilkins *et al.,* 2017). Although CVD related mortality is now declining in most of Europe, there are about 49 million people living with CVD in the EU with a cost of some €210 billion/year (Wilkins *et al.,* 2017). In addition, since 1996, the number of people diagnosed with type 2 diabetes in the UK has increased from 1.4 million to almost 3.5 million with currently about 700 new cases confirmed each day (Diabetes UK, 2016). Diet is a key risk modifying factor for chronic diseases and this must be used appropriately throughout the various life stages not least because reducing risk in early life can have benefits in later life.

This paper aims to identify some of the age-related chronic disease-nutrition associations that are currently causing concern and what role milk/dairy foods and red and processed meat may play in their development or prevention.

Children and teenagers: nutritional effects on adult health

There is increasing evidence that diets during childhood and adolescence can impact on health in later adulthood. For example, it has been known for some time that undernutrition in childhood leading to stunted growth, is associated with increased risk of hyperglycaemia, hypertension, elevated blood lipids and obesity in adulthood (de Onis and Branca, 2016). Despite recent worldwide improvements, stunting in sub-Saharan Africa remains about 40 % and some countries have an even higher prevalence (Semali *et al*., 2015). It is of note that both meat and milk have been identified as key foods for reducing stunting in children. In a cross-sectional study with young children in Guatemala, Democratic Republic of Congo, Zambia, and Pakistan, Krebs *et al*. (2011) showed that consumption of meat (which included chicken and liver but not fish) was associated with a substantial reduced risk of stunting (odds ratio: 0.64, 95% CI: 0.46, 0.90). More recently, Michaelsen (2013) emphasised that milk has a specific growth promoting effect in children, an effect which is seen in both developing and developed countries, indicating an effect even when energy and nutrient intake is adequate, possibly related to the stimulating effect of insulin-like growth factor 1. It is also noteworthy that in a longitudinal study of children from the south of England, Morgan *et al*. (2004) showed that meat intake (red and white combined) from 4 to 12 months was positively and significantly associated with body weight gain and with measures of psychomotor development. The relative effects of red and white meat were not reported, but the authors suggested that the meat protein may have produced the effect on growth, whilst the supply of arachidonic acid from the meat may have been responsible for the improvements in psychomotor development. They were unable to identify any effects of iron or zinc and there was no interaction between meat intake and breast feeding.

There is also increasing evidence on the importance of maintaining optimal cardiovascular health from birth through childhood and beyond to reduce the risk of CVD in later adulthood with the emphasis on diet and adequate exercise (Steinberger et al., 2016). It is therefore of interest that dairy consumption is inversely and longitudinally associated with childhood obesity and overweight (Lu *et al*., 2016).

There is a particular concern about the mineral intakes of children. About 70 % of bone weight is accounted for by calcium phosphate and thus adequate dietary calcium supply is essential to permit optimal bone growth. A sub-optimal calcium intake reduces bone density more quickly than it affects growth (Moore *et al.,* 1963) and radiographic evidence of rickets has been found in children with a low calcium intake, despite adequate vitamin D status (Root, 1990). As shown in Figure 1 almost 20% of UK females aged 11-18 years have calcium intakes below the Lower

Reference Nutrient Intake (450 mg/day) and this is linked to a marked reduction in milk consumption after the age of about 10 years (Bates *et al.,* 2014). This is supported by the study of Black *et al.* (2002) which showed in growing children in New Zealand, that long-term avoidance of milk was associated with small stature and poor bone health and by a recent Spanish study (Rubio-López *et al*., 2017) which found in children that girls were more likely to have a sub-optimal calcium intake than boys and that in both genders a low calcium intake (649 mg/day) was associated with significantly lower height and height z-score than those with an adequate calcium intake (1081 mg/day). A two year milk intervention study with 757 Chinese girls initially aged 10 years compared those who consumed 330 ml calcium-fortified milk on school days with those who additionally had a vitamin D supplement and a control group which had neither. The consumption of the milk, with or without added vitamin D gave rise to significantly greater rate of height increase, body weight, total bone mineral mass and bone mineral density. Over the intervention period mean calcium intake was 649, 661 and 457 mg/d for the milk, milk plus vitamin D and control groups respectively (Du *et al.,* 2004). A more recent study with Chinese children showed increased bone mineral density in the femoral neck as a result of a high (~1250 mg/d) vs low (~700 mg/d) calcium intake over a one year period (Ma *et al*., 2014). The authors suggest that calcium supplementation to increase bone mineral mass is more effective in early puberty than in late puberty and that children should be encouraged to increase weight-bearing exercise which augments the effect of calcium. The evidence for effects of milk/calcium on bone development in children is fairly strong but it is less certain whether the benefits are carried into adulthood.

The recent US National Osteoporosis Foundation's position statement on peak bone mass development (Weaver *et al.,* 2016) emphasises that bone mineral accretion rate becomes rapid around the time of puberty and reaches its maximum a little after maximum height gain. Weaver *et al*. (2016) reported that for children of European ancestry, maximum bone mineral accretion rate occurs at age of 12.5 ± 0.90 years for females and 14.1 ± 0.95 years for boys, and emphasised that sub-optimal bone mineral accretion in teenage years increases the risk of osteoporotic fractures in later life, particularly for post-menopausal women. This concept is supported by the work of Kalkwarf *et al*. (2003) who used data on 3251 white females in the US National Health and Nutrition Examination Survey and showed that milk consumption in childhood and adolescence was positively associated with bone mass in older age and negatively associated with osteoporotic fracture after 50 years old. Interestingly, the association between childhood milk intake and fracture rate was greater than for milk intake during adolescence. However this study used dietary recall from adulthood back to childhood and the validity of this has been questioned.

A marked fall in milk consumption particularly in adolescence is no doubt a key contributor to the observed sub-optimal calcium intake by many UK children, and the study of Black *et al*. (2002) showed that male and female New Zealand children with a long history of milk avoidance had poor bone health with small bones, low areal bone mineral density and volumetric bone mineral apparent density, and a high prevalence of bone fractures. Sub-optimal calcium intake may extend beyond childhood and a two year prospective cohort study aimed to identify nutrients, foods and dietary patterns associated with stress fracture risk and changes in bone density in 125 female competitive distance runners aged 18-26 years (Nieves *et al*., 2010).

The results showed that 17 subjects had at least one stress fracture during the follow-up period and that higher intakes of calcium, skimmed milk and dairy products were associated with lower rates of stress fracture. Each additional cup of skimmed milk drunk per day was associated with a 62 % reduction in stress fracture incidence (P<0.05) and a dietary pattern of high dairy products and low fat intake was associated with a 68 % reduction (P<0.05) as well as increased bone mineral density (P<0.05).

A recent study in the USA indicated that except for children and adolescents with very low calcium intakes, magnesium intake may be more important in relation to bone development (Abrams *et al*., 2013). The study was based on 63 healthy children aged four to eight years, none of whom were taking vitamin or mineral supplements. The results showed that although calcium intake was not significantly associated with total bone mineral content or density, intake of magnesium and the amount absorbed were key predictors of bone mass. This is supported by a recent study in men which showed that low serum magnesium was strongly and independently associated with increased fracture risk (Kunutsor *et al*., 2017). Milk/ dairy products are key sources of magnesium and many children in the UK have a considerably sub-optimal magnesium intake, more so than for calcium (Figure 1).

The data on sub-optimal calcium and possibly also magnesium are a substantial concern, particularly since most of Europe is now of sub-optimal vitamin D status (Cashman *et al*., 2016). It is therefore concerning that childhood rickets, which in the UK essentially disappeared in the early-mid 20th century, has reappeared in recent times. The number of cases is low with the UK National Health Service recording about 700 cases in England in 2013/14 (NHS Choices, 2017a) but is clearly a concern given the dietary data reviewed above. The recent study of Sahni *et al.* (2017) using older, mainly non-Hispanic men and women (mean age 75 years) in the Framingham Osteoporosis Study cohort is noteworthy. This showed that higher intakes of milk and milk + yoghurt + cheese were associated with higher lumber spine bone mineral density at baseline, and after a 4-year follow up a higher intake of milk + yoghurt + cheese was protective of trochanter bone mineral density but crucially, both beneficial outcomes were only seen in those subjects consuming a vitamin D supplement (16.0 µg/d vs. 5.3 µg/d in non-consumers). Surprisingly, vitamin D status was not measured and the effects were seen in both men and women. The study suggests that skeletal benefits of dairy consumption can occur in older subjects even over relatively short periods but this is dependent on vitamin D intake.

Also of interest is a very recent study showing an inverse association between dairy calcium and dairy vitamin D intake and the risk of early menopause (Purdue-Smithe *et al*., 2017). The effect was not seen with supplemental calcium and vitamin D, leading the authors to suggest that it is likely that other constituents of dairy foods may also be involved in menopause timing.

Iodine status during pregnancy

Until recently it has been assumed that the UK population was of adequate iodine status. However, more recently a study in UK schoolgirls showed 51% to be classified as mildly iodine deficient based on urinary iodine concentrations

(Vanderpump *et al.*, 2011) and the UK National Diet and Nutrition Survey (Bates *et al.*, 2014) reports that on average, young females aged 11 to 18 years consume only 81% of the RNI for iodine and that 22% of young females have iodine intakes below the Lower RNI of 70 µg iodine/d (Figure 1). Importantly, a study in a large UK cohort of women during pregnancy showed consistent mild-to-moderate iodine deficiency (Bath *et al*., 2014a) with similar findings in pregnant Norwegian women (Brantsæter *et al*., 2013) and in UK women of childbearing age (Bath *et al*., 2014b). Moreover, a number of studies have now shown an association between low maternal iodine status in early pregnancy and poorer cognitive performance in the children (Bath *et al*., 2013; Hynes *et al.,* 2013). It would seem very important that a randomised controlled trial be carried out with mildly iodine deficient women during pregnancy together with a subsequent longitudinal follow-up of their children. Not only would this give more definitive evidence on the effect of mild deficiency but it would also provide important information on the need for supplementary iodine during pregnancy. There are however doubts that ethical considerations would allow such a study to be undertaken.

Milk and dairy foods are the largest dietary source of iodine in the UK providing 40 and 39 % of the daily intake of iodine for 11-18 year old males and females respectively (Bates *et al.*, 2014). Interestingly, milk and dairy product intake was also shown to be the most important determinant of iodine status in US men and women, despite the availability of iodised salt (Lee *et al*., 2016). Survey studies on UK milk iodine concentrations undertaken in recent times (Food Standards Agency, 2008) do not suggest that in the UK milk iodine concentration has declined but they do show that milk produced in the summer has on average, a 50% lower iodine concentration than winter milk. Moreover, four UK studies (Food Standards Agency, 2008; Bath *et al*., 2012; Payling *et al*., 2015; Stevenson *et al*., 2018) reported that milk from organic dairy systems had significantly lower iodine concentrations than from conventional systems. There is good evidence that the iodine intake by the dairy cow has the major influence on milk iodine concentration, and since most iodine would be provided in supplementary feeds, this would explain the effects of summer and organic systems since both are likely to be associated with less supplementary feeding. This and other factors which influence milk iodine concentration are discussed in detail by Flachowsky *et al.* (2014).

These findings clearly have implications for human iodine intake and status although the major impact on iodine status of young UK females is likely to be a result of marked reduction in milk consumption. It is of note that in the study of Bath *et al.* (2014a), only women consuming more than 280 ml of milk/day were of adequate iodine status.

Iron and zinc status of young women

Ferritin is the major storage protein in body cells and there is a clear relationship between the amount of stored iron in the body and serum ferritin concentration. Serum ferritin concentration is also used as an indicator of iron status, with the WHO (2011) definition of iron deficiency being a concentration less than 15 µg/L for males and females aged 5 years and over. Based on Years 1-4 of the rolling National Diet and Nutrition Survey (Bates *et al*., 2014), Figure 2 shows that more than 25% of UK females in the age range 11-18 years have serum ferritin concentrations less than 15 μg/L with 15% of older females (19-64 years) also being of the sub-optimal status. Within that age range pre-menopausal women will be of lower status than those that are post-menopausal.

There has been a continued decline in red meat consumption over the last 40 years and the more recent data on the association between red/processed meat and colo-rectal cancer may have accelerated the trend. Using adjusted National Food Survey data 1974 to 2000, Expenditure and Food Survey 2001-02 to 2007 and Living Costs and Food Survey 2008 onwards, DEFRA (2015) reported that red meat (beef, sheep meat, pork) consumption had declined from 413 g/person/week in 1975 to 195 g/person/week in 2014. This has been associated with a decline in iron intake with Heath and Fairweather-Tait (2002) reporting that it has fallen from about 13.5 mg/person/day in 1970 to about 10 mg/person/day in 1998. The meat and iron intakes given above are based on family food purchases and therefore do not give precise intake data by age or gender. It is however, of interest to note that Years 1-4 of the rolling National Diet and Nutrition Survey (Bates *et al*., 2014) shows that relative to an RNI of 14.8 mg/d, mean iron intake of females aged 11 to 18 years of age is only 8.4 mg/day and that the greatest source of dietary iron is from cereals and cereal products (48%) with meat and meat products only contributing 18%. Although efficiency of iron absorption is highly regulated according to the metabolic need for iron, the source of dietary iron is still important. Not only is haem iron from red meat some 2 to 6 times more bioavailable than non-haem iron, but meat also enhances the absorption of non-haem iron (Geissler and Singh, 2011).

The long-term consequences of sub-optimal iron intake and status are unclear. SACN (2010) noted that early functional deficiencies have been seen in subjects with serum ferritin concentrations below 16 to 20 µg/L and haemoglobin values at or below 110-120 g/L. The evidence points to girls and women of child-bearing age being at the greatest risk and SACN (2010) recommended that health practitioners pay particular attention to the increased risk of iron deficiency anaemia in these populations.

Figure 1 shows that about 20% of UK females (11-19 years) have zinc intakes below the LRNI. Meat, and particularly red meat, is the greatest single source of dietary zinc in that age group and gender (Bates *et al*., 2014) and as noted above this has declined substantially over the last 40 years (DEFRA, 2015). The prospective risks of sub-optimal zinc status are not certain. A recent systematic review of prospective studies (Chu *et al*., 2016) found no association between zinc status and risk of type 2 diabetes whilst in three out of five studies, higher serum zinc concentration was inversely associated with risk of CVD. Overall, few studies were available and Chu *et al*. (2016) highlighted the need for more data before clear guidelines on zinc intake needed for reduced risk of CVD and type 2 diabetes can be given with confidence.

Dairy foods in adulthood and risk of cardiometabolic diseases

As a result of chronic positive energy balance, the prevalence of overweight is increasing rapidly in many parts of the world (Kopelman, 2000) and obesity, usually defined as a body mass index (BMI) of 30 kg/m^2 or greater, is acknowledged as a major risk factor for chronic diseases, including type 2 diabetes, CVD and cancer.

The relationship between BMI and diabetes is particularly striking, overweight and obesity alone accounting for about 70 % of type 2 diabetes (Hu *et al.,* 2001). Having examined this relationship in a US cohort of 121 000 nurses Hu *et al*. (2001) stated that '…*the majority of cases of type 2 diabetes could be prevented by weight loss.*' This highlights the importance of BMI control and understanding the differential effects of adiposity, particularly central abdominal adiposity, and diet in both prevention and treatment of type 2 diabetes.

Evidence from prospective cohort studies

Numerous studies have investigated the association of milk and dairy food intake and cardiometabolic diseases (CMD; CVD + type 2 diabetes). Whilst prospective study data are regarded as providing weaker evidence than randomised controlled trials (RCT) on the diet/food-disease relationship, they have the advantage of looking at long term effects and use real disease events as the outcome measures. Very long term RCT using disease data are impractical and would be very expensive, with the result that most RCT use markers of disease risk (e.g. LDL-C) as primary outcome measures. Meta-analysis of prospective studies is a valuable tool for looking at the overall association between dairy foods and CMD although there remains a concern that in many studies the dairy foods involved are poorly defined which limits assessment of the relative effects of different dairy foods. This is particularly so when comparing high fat vs. low fat dairy products for which there are no universally agreed definitions. Aspects of this work were reviewed by Lovegrove and Hobbs (2016).

Early meta-analyses of prospective cohort studies reported that overall, high milk consumption does not increase the relative risk (RR) of coronary heart disease (CHD) (Mente *et al*., 2009; Elwood *et al*., 2010). The meta-analysis of Mente *et al.* (2009) using data combined from prospective cohort and clinical studies, indicated no significant increase in the RR of CHD in high vs. low milk consumers (RR 0.94; 95% confidence interval (CI) 0.75-1.13). Whilst there have been several other meta-analyses over recent times, a series has been recently published examining the dose-response association between dairy food consumption and type 2 diabetes (Gijsbers *et al.,* 2016), stroke (de Goede *et al*., 2016), and CVD and all-cause mortality (Guo *et al.,* 2017), and these are probably the most definitive currently available. The outcomes of these meta-analyses are summarised in Table 1. Overall, these show no increase in risk of CVD per unit increase in milk and cheese consumption and a significant reduction in risk of stroke per unit intake of cheese and milk. The association of yoghurt with a reduced risk of type 2 diabetes is of particular interest given the large ongoing increase in its prevalence. The beneficial effect of yoghurt and other fermented dairy foods was also seen in the EPIC-InterAct study (Sluijs *et al*., 2012). Some studies (Mozaffarian *et al*., 2013) have shown an inverse association between circulating *trans*-palmitoleic acid (16:1 *n*-7) and incident type 2 diabetes, although whether the effect of this fatty acid is causative or simply a marker of dairy food consumption is unclear. There are relatively few studies which have looked at the effects of butter on CMD but the recent dose-response meta-analysis of Pimpin *et al*. (2016) indicates no significant association between butter consumption and all-cause mortality, CVD, CHD and stroke although there was a significant negative association with type 2 diabetes (Table 2). The meta-analysis of

Pimpin *et al.* (2016) involved relatively few cohorts for CVD (n=4), CHD (n=3), stroke (n=3) although 11 cohorts were suitable for inclusion for type 2 diabetes.

Given the evidence linking saturated fatty acids (SFA) with low density lipoprotein cholesterol (LDL-C) and LDL-C with CVD and the fact that dairy foods are major contributors to SFA, the consistent neutral or beneficial associations between dairy foods and CVD from analysis of prospective data remains something of a paradox to many. There is however increasing evidence that goes some way to explain the effects seen in meta-analysis of prospective studies.

Hypertension is one of the major risk factors for CVD development and stroke in particular, and in the UK up to 30% of adults are hypertensive (Townsend *et al.*, 2015). It is influenced by gene polymorphisms, nutrition, the environment and interactions between these factors. Milk and milk derived products provide essential micronutrients (e.g. calcium, magnesium, iodine and vitamin D) and proteins (whey, casein and specific bioactive peptides) some of which have been associated with beneficial hypotensive effects, either independently or synergistically (Kris-Etherton *et al.,* 2009). A recent chronic RCT (Fekete *et al*., 2016) showed that whey protein had a greater hypotensive effect than casein and the effects were seen on both central and peripheral blood pressures. A number of mechanisms by which milk and its components could lower blood pressure (BP) have been proposed (Fekete *et al*., 2013). Peptides released during digestion of casein and whey proteins have been shown to have hypotensive effects by inhibiting the action of the angiotensin-I-converting enzyme, resulting in vasodilation (Fitzgerald and Meisel, 2000), by modulating the release of endothelin-1 by endothelial cells (Maes *et al*., 2004) and acting as opioid receptor ligands increasing nitric oxide production which mediates arterial tone (Kris-Etherton *et al*., 2009). There is little firm evidence whether there are differential effects of low vs. high fat dairy foods and whilst Engberink *et al.* (2009) reported an inverse association between low fat dairy intake and risk of hypertension in older adults, others have shown that both low and high fat products have hypotensive effects (Ralston *et al*., 2012). In addition, results from the Caerphilly Prospective Study showed that when compared with non-milk consumers, men who consumed >586 ml/d had on average a 10.4 mmHg lower systolic BP after a 22.8 year follow-up (Livingstone *et al*., 2013). Some of the inconsistencies between studies may well relate to the lack of a consistent definition of what constitutes low and high fat dairy foods.

Other factors which may counterbalance the effects of SFA in dairy foods include evidence that milk proteins, and whey protein in particular, can reduce plasma concentrations of both total cholesterol and LDL-C and triacylglycerols (Fekete *et al*., 2016). This may be an important effect although more details are needed including a meta-analysis of effects of milk proteins on blood lipids (Lovegrove and Givens, 2016). Also, as recently reviewed by Thorning *et al.* (2017), the so-called food matrix effect, particularly of cheese, can reduce the amount of dairy fat that is digested leading to a moderation of the rise in blood cholesterol. This may in part explain the prospective observation of de Oliveira *et al.* (2012) that the effects of SFA from dairy and meat differ. They estimated that the replacement of 2% of SFA energy from meat (including red and processed meat, fish, and poultry) with that from dairy (excluding butter) was associated with a 25% lower risk (as hazard ratio; HR) of CVD (HR: 0.75, 95% CI: 0.63, 0.91).

There is now good evidence that arterial stiffness, especially of the large vessels is an important predictor of CVD effects (Cockcroft and Wilkinson, 2000) and this can be affected by dietary patterns (Kesse-Guyot *et al*., 2010). The measurement of carotid-femoral pulse wave velocity (PWV) is regarded as the gold standard for assessing arterial stiffness and can independently predict CVD events (Van Bortel *et al.,* 2012). Livingstone *et al.* (2013), using data from the Caerphilly Prospective Study, showed for the first time in a longitudinal study, that dairy product consumption (not including butter) does not increase PWV (which would indicate increased arterial stiffness). Moreover, the measurement of augmentation index, another indicator of arterial stiffness, was lower in men with the highest dairy consumption (Livingstone *et al.,* 2013). An Australian cross-sectional study also reported that consumption of dairy foods was negatively associated with PWV (Crichton *et al.,* 2012).

Modifying the diet of the dairy cow to replace saturated fatty acids in milk fat.

It is now clear that the effects of reducing dietary SFA are best predicted by an understanding of what replaces them. Reduced risk of CVD has been associated with replacement of SFA with polyunsaturated fatty acids (PUFA) (Micha and Mozaffarian, 2010; Siri-Tarino *et al*., 2015) and *cis*-monounsaturated fatty acids (*cis*-MUFA) (Vafeiadou *et al.,* 2015). This raises the question of whether CVD risk would be reduced if a proportion of SFA in dairy fat was replaced with *cis*-MUFA and/or PUFA. The few RCT that have examined this in detail were reviewed by Livingstone *et al*. (2012) with the conclusion that based on blood cholesterol changes, it was probable that CVD risk would be reduced from consumption of milk and dairy products containing fat with a proportion of SFA replaced mainly by *cis*-MUFA although the evidence available was very limited in nature. An ongoing RCT (RESET; ClinicalTrials.gov NCT02089035; Vasilopoulou *et al*., 2016) is studying this in depth.

Meat consumption and chronic diseases

The evidence on the association of meat consumption with the various chronic diseases has been somewhat inconsistent, in part due to variability in the definition of the different meat types and because of compositional variability within the various meat types. Normally, white meat relates to meat which is light coloured before cooking and includes poultry meat and fish and occasionally pork (Oostindjer *et al*., 2014), whereas the World Health Organisation (WHO, 2017) defines red meat as mammalian muscle meat, including, beef, veal, pork, lamb, mutton, horse, and goat. In particular there has been confusion about what constitutes processed meat. WHO (2017) defines processed meat as meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. This definition has been broadly adopted by organisations which study the association between processed meat and risk of CMD and cancer (WHO, 2017).

The current review is restricted to consideration of the health effects of red meat and processed meat.

Red and processed meat consumption in adulthood and risk of cardiometabolic diseases

The meta-analysis of Micha *et al*. (2010) found that intake of processed meat, but not red meat, was associated with a higher risk of CHD (RR per 50g/day: 1.42, 95%CI: 1.07, 1.89). The recent study with two Swedish Cohorts (Bellavia *et al*., 2016), reported that those subjects in the highest quintile of red meat consumption compared with those in the lowest had a 21% increased risk of all-cause mortality (HR: 1.21, 95% CI: 1.13, 1.29) and a 29% increased risk of CVD mortality (HR: 1.29, 95% CI: 1.14, 1.46). In the study of Würtz *et al*. (2016) with two Danish cohorts, replacing red meat with vegetables in females reduced the risk of CHD (HR: 0·94, 95% CI: 0·90, 0·98) whereas replacing fatty fish with vegetables showed an increased risk of CHD (HR: 1·23, 95% CI: 1·05, 1·45), whilst replacing poultry meat by vegetables did not lead to a change in CHD risk (HR: 1·00, 95% CI: 0·90, 1·11). Similar, but mostly non-significant results were seen in males which the authors suggest may be due to a higher baseline risk in men such that relative associations would be weaker although no doubt there may be other factors. Overall, the findings suggest that replacing red meat with vegetables (or potatoes) is associated with a reduced CHD risk.

The prospective based evidence on the link between red and processed meat consumption and type 2 diabetes overall shows a positive association. The meta-analysis of Micha *et al.* (2010) reported that whilst processed meat gave rise to a 19% higher risk of type 2 diabetes (RR: 1.19, 95%CI: 1.11, 1.27), red meat consumption did not change the risk. The results from the EPIC-InterAct study (InterAct Consortium, 2013) with 340,234 adults from eight European countries showed positive associations with type 2 diabetes cases for increasing intake of total meat (HR per 50g/d: 1.08, 95% CI: 1.05, 1.12), red meat (HR per 50g/d: 1.08, 95% CI: 1.03, 1.13) and processed meat (HR per 50g/d: 1.12, 95% CI: 1.05, 1.19). In a cohort of males (26,357) and two cohorts of females (total 122,786) Pan *et al*. (2013) reported that compared with the reference group with no change in red meat consumption, increasing red meat consumption by more than 0.5 portions per day was associated with a large increase in risk of type 2 diabetes (HR: 1.48, 95% CI: 1.21, 1.41). Reducing red meat by more than 0.5 portions per day produced a reduced risk (HR: 0.86, 95% CI: 0.80, 0.93).

Overall, the evidence of a positive association between red meat and processed meat consumption and risk of type 2 diabetes is building, although more and mechanistic evidence is needed, especially for processed meat. Given the large increase in prevalence of type 2 diabetes, the effect of meat consumption needs much more attention, not least with data that allow a dose-response effect to be estimated.

Dairy, red meat and processed meat consumption in later adulthood and risk of cancer

The World Cancer Research Fund (WCRF) together with the American Institute for Cancer Research (AICR) published their major report 'Food, Nutrition, Physical Activity, and the Prevention of Cancer in 2007 (WCRF/AICR, 2007). Subsequently they started a continuous programme updating the evidence at regular intervals. It is therefore not the intention of this paper to review this very substantial topic in detail, rather to highlight key issues which have emerged from the WCRF/AICR (2007) report and the subsequent updates, but limited to colorectal cancer, the most prevalent type that affects both men and women, together with prostate and breast cancer, the key gender-specific types. Almost all of the evidence is based on data from prospective studies together with meta-analysis. Table 2 summarises the latest data from WCRF/AICR in terms of dose-response meta-analysis giving RR and 95% CI. Table 2 does not give the number of studies, subjects or disease events or degree of heterogeneity in the various meta-analyses and the source reports should be consulted for these data which are needed to fully interpret the RR values.

Dairy foods and risk of cancer

The WCRF/AICR (2007) report stated that milk consumption probably protects against colorectal cancer (RR: 0.78, 95 % CI: 0.69, 0.88). This was updated in the report of WCRF/AICR (2010) where meta-analyses showed a 9 % reduced risk per 200g/d for colorectal cancer with a similar direction though non-significant effects for colon and rectal cancers (Table 2). The WCRF/AICR (2010) report was updated by Aune *et al*. (2012) based on a total of 19 cohort studies, containing just over one million subjects, of which 11,579 developed colon cancer. The summary RR were 0.83 (95 % CI: 0.78, 0.88) per 400 g/day of total dairy products and 0.91 (95 % CI: 0.85, 0.94) per 200 g/day of milk intake. Overall, the results confirmed earlier work that total dairy products and milk, but not cheese or other dairy products (mainly butter, yoghurt, ice cream and fermented milk), are associated with a reduced risk of colorectal cancer.

The report of WCRF/AICR (2007) indicated that data on any association between dairy food consumption and risk of breast cancer were very limited and as a result did not provide any conclusions. Dong *et al*. (2011) identified 18 cohort studies with 24 187 breast cancer cases and 1 063 471 women which were suitable for meta-analysis. They reported that increased consumption of total dairy foods except milk, may be associated with a reduced risk of breast cancer (RR: 0.85; 95% CI: 0.76–0.95). There were some indications of a stronger association with low fat dairy products and for pre-menopausal women. The most recent update on dairy foods and breast cancer has been published very recently (WCRF/AICR, 2017) and is summarised in Table 2. The overall conclusion is that for pre-menopausal breast cancer, despite limited data, there was evidence of a significant reduction in risk associated with consumption of total dairy products but not for milk. For post-menopausal breast cancer there were too few data to reach a firm conclusion.

The WCRF/AICR (2007) reported that total dairy was associated with a possible increase in prostate cancer (RR: 1.06 per serving/d, 95 % CI: 1.01, 1.11) whilst milk was associated with a substantial increased risk of advanced prostate cancer (RR: 1.30, 95 % CI: 1.04, 1.61). The more recent update report WCRF/AICR (2014) has moderated the earlier findings somewhat with total dairy and milk showing no significant association with the three prostate cancer types examined (Table 2). There was however, an association with increased risk for low fat milk (RR: 1.06 per 200g/d, 95% CI: 1.01-1.11) and cheese (RR: 1.09 per 50g/d, 95% CI: 1.02-1.18). The overall conclusion of the report was that '*for a higher consumption of dairy products, the evidence suggesting an increased risk of prostate cancer is limited'.*

Meat and processed meat and risk of cancer

WCRF/AICR (2007) concluded that the evidence was 'convincing' that red meat and processed meat were causes of colorectal cancer (CRC). The evidence was updated by WCRF/AICR (2010) with data from a further six red meat and 11 processed meat studies. The results from this report are summarised in Table 2 and broadly agree with the 2007 report but highlight that the risk of colorectal cancer associated with processed meat is approximately twice that of red meat. More recently The International Agency for Research on Cancer (Bouvard *et al*., 2015) summarised the conclusions of an expert working party which were broadly in line with those of WCRF/AICR (2010) classifying processed meat as '*carcinogenic to humans*' and red meat as '*probably carcinogenic to humans*'.

In response to the evidence of WCRF/AICR (2010) the UK Government published public advice on meat consumption which remains today (NHS Choice, 2017b). The advice is for those who consume more than 90 g/d of cooked red and processed meat is to reduce this to 70 g/d. Based on detailed data collected by the UK National Diet and Nutrition Survey (Bates *et al*., 2014), the UK's Agriculture and Horticulture Development Board confirmed that the UK mean intake of red meat is 54 g/d and 17 g/d of processed meat, in compliance with the guidelines (AHDB, 2015). There is of course considerable variability around these values and the guidelines are of greatest relevance to those with intakes considerably in excess of the advice especially if consumption of processed meat is high. However there remains considerable uncertainty about the risks associated with specific types of red meat (e.g. pork vs beef) and processed meat and indeed what is processed and what is not. It is also noteworthy that the recent report on stomach cancer (WCRF/AICR, 2016), concluded that there is *'strong evidence that consuming processed meat increases the risk of stomach non-cardia cancer'*.

Despite the relatively consistent outcomes from meta-analysis of prospective studies, the causative mechanisms whereby red meat and processed meat increase the risk of CRC remains unclear. Studies in rodent models suggest a role for dietary haemoglobin since it and red meat promote the development of aberrant crypt foci, a generally agreed pre-cancer feature. Haem may catalyse the endogenous production of *N*-nitroso compounds and certain aldehydes both of which are carcinogenic (Alexander *et al*., 2015).

The recent study of Carr *et al*. (2017) is also of interest. This was a case–control study with 2 449 cases and 2 479 controls with information on risk factors of CRC and a completed food frequency questionnaire. The study showed that both red meat and processed meat consumption were associated with increased risk of CRC (>1 time/day vs <=1 time/ week, OR 1.66, 95% CI 1.34, 2.07) although the risk was somewhat higher for processed meat than red meat. There were no major differences amongst the various molecular tumour characteristics measured, although the risk of KRAS-mutated CRC was lower (>1 time/day vs <=1 time/ week, OR 1.49, 95% CI 1.09, 2.03) than for the KRAS-wild type CRC (>1 time/day vs <=1 time/ week, OR 1.82, CI 1.42, 2.34). The findings provide further evidence on the association between red and processed meat and CRC with the risk being similar for colorectal sub-sites and most of the investigated molecular characteristics although some differences were seen in specific sub-types. It remains clear that considerably more research is needed in this area.

Table 2 also summarises any association of breast cancer with red and processed meat based on WCRF/AICR (2017). There was no significant association of pre- or post-menopausal breast cancer with red or processed meat although there was only a limited number of studies and considerable heterogeneity between some studies.

Sustainability of producing dairy foods and red meat

The environmental cost of food production and its impact on the sustainability of food supply has gained much attention in recent times. It is not the intention to explore this in detail, rather to highlight the importance of balancing sustainably metrics with the need for diets that are not only nutritionally adequate but also provide health functionality.

Audsley *et al.* (2009) estimated that the UK food supply chain was responsible for about 20% of all greenhouse gas emissions (GHGE) and that 56% of these result from primary production, farming in particular, with methane and nitric oxides accounting for in excess of 50%. They also estimated that ruminant meat production was responsible for about 75% of GHGE in the UK resulting from changes in land use. Overall, red meat production had the highest environmental impact of all the food groups considered followed by milk products. It is of note however that they also concluded that attempts to reduce GHGE from food production and consumption by the UK target of 70% (Garnett, 2008) by focusing on one solution such as eliminating meat and dairy foods from the national diet, would not provide the reductions needed. Nevertheless, dietary scenarios for reducing environmental impact of UK diets have typically reduced ruminant (red) meat and dairy food consumption to 20-30% and 50-60% of the then typical consumption respectively (Audsley *et al.,* 2009), but crucially there is no evidence regarding the potential human health benefits of such reductions.

The Danish OPUS study was set up to assess the feasibility of a national diet that was not only healthy but environmentally friendly (Mithril *et al*., 2012). It is of note that that the ‘New Nordic Diet’ (NND) contained slightly more (101%) dairy products than the average Danish diet (ADD) but had large reductions in meat, particularly of beef (30% of ADD). These changes were also driven by a desire to reduce imports of most foods to zero (Saxe, 2014). Despite assessing that the NND provided energy and nutrient intakes meeting the Nordic Nutritional Requirements, small adjustments were made based on evidence of health-related food functionality (Mithril *et al*., 2012). In addition, and perhaps uniquely, a long term (26 weeks) human intervention study was performed which showed that compared with the ADD, the NND induced weight loss and also reduced blood pressure, blood cholesterol and triacylglycerols (Poulsen *et al*., 2014). Moreover, at the end, a further 12 months study was carried out where both groups of subjects had access to NND, to investigate the effect of the NND in a free-living setting. It was shown that despite some weight regain, this was lower in those with high compliance to NND, and the NND effects on blood pressure were essentially maintained. Whilst consumers reported that the NND provided greater dietary satisfaction, this study also highlighted the major challenges of translating prescribed diets into everyday life (Poulsen *et al*., 2015).

Conclusions

Overall it is clear that milk and dairy foods are key sources of important nutrients and the concentration of some key nutrients such as iodine can be influenced by the method of primary production. The reduction in milk consumption particularly by females during teenage years is concerning and may already have had serious consequences in terms of bone development which may not become apparent until they are in later life. Recent dose-response meta-analyses show no evidence of increased risk of CVD from high dairy consumption and the negative association of milk proteins and milk/fermented dairy with blood pressure and type 2 diabetes respectively may become very important findings, but this area needs further development as does the work on replacing a proportion of SFA in milk fat with *cis*-MUFA. The updated reports on associations between dairy foods, red meat and processed meat and various cancers provide further confidence on the inverse association of milk/dairy and colorectal cancer and no increased risk of breast cancer. The earlier information showing a significant increased risk of colorectal cancer from consumption of red and particularly processed meat, has been reinforced by more recent data although on average, consumption of red and processed meat in the UK is just within the UK government guidelines. It is also important to judge disease risk from specific foods alongside risks associated with other lifestyle choices and to be aware that information on the underlying disease risk is needed to allow the effect of relative risks on absolute risk to be calculated. There is also an ongoing need to make judgments about the sustainability of food production. Based on the current evidence, it seems essential that dietary pattern, nutrition and health-related functionality are included in any debate on this important subject.

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Software and data repository resources

All published papers are archived in CentAUR (http://centaur.reading.ac.uk/), the University of Reading's searchable electronic archive for research publications and outputs. Members of the public can access bibliographic details and many refereed full text versions free of charge, for personal research or study, in accordance with the University's End User Agreement.

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Table 1. Recent dose-response meta-analyses examining the relative risk (RR) of cardiometabolic disease (CVD) in relation to consumption of dairy foods.

Dairy food	Outcome	RR (95% CI*)	Reference
Milk/244g/d	All-cause mortality	1.00 (0.93-1.07)	Guo *et al*. 2017
Milk/244g/d	CVD	1.01 (0.93-1.10)	Guo *et al*. 2017
Cheese/10g/d	CVD	0.98 (0.95-1.00)	Guo *et al*. 2017
Yoghurt/50g/d	CVD	1.03 (0.97-1.09	Guo *et al*. 2017
Milk/200g/d	Stroke	0.93 (0.88-0.98)	De Goede *et al*. 2016
Cheese /40 g/d	Stroke	0.97 (0.94-1.01)	De Goede *et al*. 2016
Yoghurt/80g/d	Type 2 diabetes	0.86 (0.83-0.90)	Gijsbers *et al.* 2016
Butter/14g/d	All-cause mortality	1.01 (1.00-1.03)	Pimpin *et al*. 2016
Butter/14g/d	CVD	1.00 (0.98-1.02)	Pimpin *et al.* 2016
Butter/14g/d	CHD	0.99 (0.96-1.03)	Pimpin *et al*. 2016
Butter/14g/d	Stroke	1.01 (0.93-0.99)	Pimpin *et al.* 2016
Butter/14g/d	Type 2 diabetes	0.96 (0.93-0.99)	Pimpin *et al.* 2016

*Confidence interval

Table 2. Dose-response meta-analyses examining the relative risk (RR) and 95% confidence interval of certain cancers in relation to consumption of red and processed meat, dairy foods and alcohol based on the findings of World Cancer Research Fund International / American Institute for Cancer Research (WCRF/ACIR).

Food/drink	Colorectal cancers (CRC)[1]			Breast cancer (BC)[2]		Prostate cancer (PC)[3]		
	All CRC	Colon	Rectal	PRM[4]	POM[5]	NA[6]	ADV[7]	FL[8]
Red and processed meat/100g/d	1.16 (1.04-1.30)	1.21 (1.06-1.39)	1.31 (1.13-1.52)	ND[9]	1.00 (0.88-1.13)		Limited evidence	
Red meat/100g/d	1.17 (1.05-1.31)	1.12 (0.97-1.29)	1.18 (0.98-1.42)	1.04 (0.84-1.29)	1.11 (0.97-1.27)		Limited evidence	
Processed meat/50g/d	1.18 (1.10-1.28)	1.24 (1.13-1.36)	1.12 (0.99-1.28)	1.02 (0.84-1.24)	1.13 (0.99-1.29)		Limited evidence	
Total dairy /400g/d for CRC, PC /200g/d for BC	0.85 (0.81-0.90)	0.92 (0.80-1.05)	1.13 (0.85-1.49)	0.95 (0.92-0.99)	0.97 (0.93-1.01)	1.09 (1.00-1.18)	0.97 (0.91-1.05)	1.11 (0.92-1.33)
Milk/200g/d	0.91 (0.86-0.97)	0.91 (0.83-1.00)	0.98 (0.82-1.17)	0.97 (0.88-1.06)	1.01 (0.97-1.04)	1.06 (1.00-1.13)	0.98 (0.89-1.09)	1.04 (0.73-1.50)

[1]WCRF/ACIR (2011); [2]WCRF/ACIR (2017); [3]WCRF/ACIR (2014)
[4]Premenopausal; [5]Postmenopausal; [6]Non-advanced; [7]Advanced; [8]Fatal; [9]No data given

Figure captions

Figure 1. Percentage of three UK population groups with micronutrient intakes less than the Lower Reference Nutrient Intake (LRNI) (from Bates *et al*., 2014).

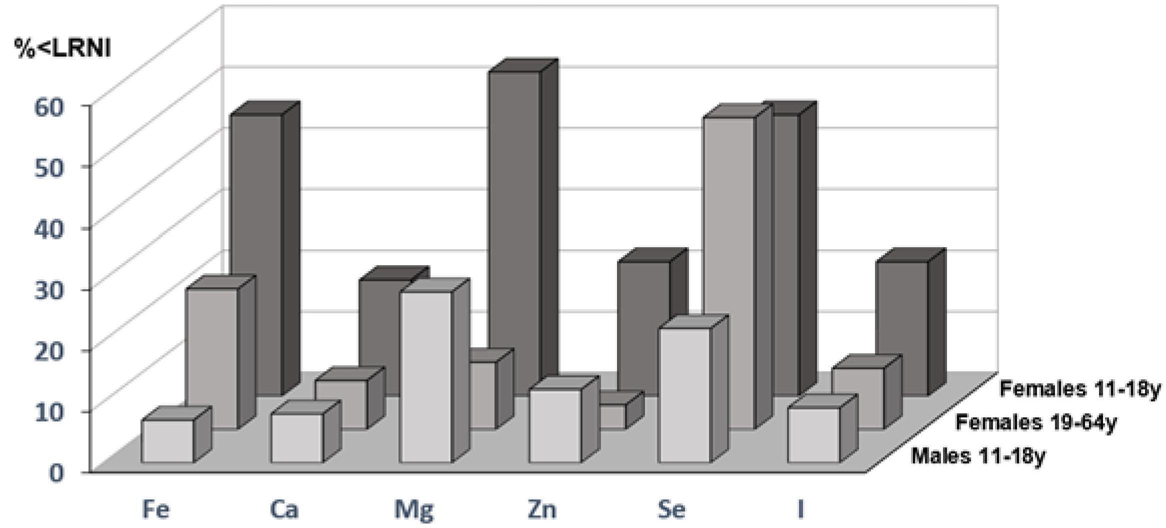

Figure 2. Percentage of UK by age and gender with serum ferritin concentrations below the threshold of adequacy of 15 µg/L (from Bates *et al*., 2014).