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MILK Symposium review: the importance of milk and dairy foods in the diets of infants, adolescents, pregnant women, adults, and the elderly

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Givens, I. ORCID: https://orcid.org/0000-0002-6754-6935 (2020) MILK Symposium review: the importance of milk and dairy foods in the diets of infants, adolescents, pregnant women, adults, and the elderly. Journal of Dairy Science, 103 (11). pp. 9681-9699. ISSN 1525-3198 doi: 10.3168/jds.2020-18296 Available at https://centaur.reading.ac.uk/94534/

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Published version at: https://doi.org/10.3168/jds.2020-18296
To link to this article DOI: http://dx.doi.org/10.3168/jds.2020-18296

Publisher: American Dairy Science Association

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Invited Review: The importance of milk and dairy foods in the diets of infants, adolescents, pregnant females, adults and the elderly.

Running head: Dairy foods in the diet at key life stages

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Interpretive summary

There is now increasing evidence that diets in early life can influence health throughout later life. Milk and dairy foods are important sources of certain nutrients and have functional effects particularly important at certain life stages. This paper examines some of the key nutrition issues during childhood, adolescence, pregnancy, middle and older age and discusses where dairy foods can be helpful. As an example, these foods can aid bone development in childhood and adolescence, maintain adequate iodine status during pregnancy and reduce muscle loss by the elderly.

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ABSTRACT

Despite an ongoing increase in life expectancy, it is not always accompanied by an increase in healthy lifespan. There is increasing evidence that dietary exposure in early life can substantially impact on chronic disease risk in later life. Milk and dairy foods are important suppliers of a range of key nutrients with some being particularly important at certain life stages. It is now recognized that milk protein can stimulate insulin-like growth factor-1 (IGF-1) essential for longitudinal bone growth and bone mass acquisition in young children, thus reducing the risk of stunting. Low milk consumption during adolescence, particularly by females, may contribute to sub-optimal intake of calcium, magnesium, iodine, and other important nutrients. Given the generally low vitamin D status of European populations, this may have already impacted bone development and any resulting reduced bone strength may become a big issue when they are much older. A sub-optimal iodine status of many young females has already been reported together with several observational studies showing an association between sub-optimal iodine status during pregnancy and reduced cognitive development by the offspring. There is now good evidence that consumption of milk/dairy foods does not lead to an increased risk of cardiovascular diseases and type 2 diabetes. Indeed some negative associations are seen, notably that between yogurt consumption and type 2 diabetes, which should be researched with urgency. Greater emphasis should be placed on reducing malnutrition in the elderly and on dietary approaches to reduce their loss of muscle mass, its functionality and bone strength. Whey protein has been shown to be particularly effective for reducing muscle loss and this needs development to provide simple dietary regimes for the elderly to follow. There is an ongoing, often too simplistic debate about the relative value of animal vs. plant food sources for protein in particular. It is important that judgements on the replacement of dairy products with those from plants also include the

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evidence on relative functionality which is not expressed in simple nutrient content (e.g. hypotensive and muscle synthesis stimulation effects). Only by considering such functionality will a true comparison be achieved.

Key words: Milk, dairy, life stage, chronic disease

INTRODUCTION

In its recent review of world health statistics, the World Health Organization (WHO, 2019) reports that global life expectancy has continued to increase, on average by 5.5 years from 2000 to 2016, although healthy life expectancy increased by only 4.8 years. There are however great discrepancies, notably that life expectancy at birth being over 18 years shorter in low income countries than in high-income countries, with a sizable proportion of the difference being related to preventable health issues. Moreover, childhood obesity continues to increase across the world but most notably in Europe and North America.

In the United Kingdom (UK), life expectancy doubled over the last 200 years and is now higher than 80 years (Roser, 2017) with an even greater population growth rate among those aged 85 years and over. Aging brings with it some important nutrition-health challenges such as increased risk of bone breakages and sarcopenia and those linked to lower absorption of vitamin B_{12} and efficiency of vitamin D synthesis. Gullberg et al. (1997) estimated the total worldwide number of hip fractures to be around 1.26 million in 1990 and they predicted this would increase to 2.6 and 4.5 million by 2025 and 2050 respectively. In support of this, Hernlund et al. (2013) reported that the frequency of osteoporotic fracture has increased in many parts of the world and proposed that in the European Union (EU), the prevalence will

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71 double by 2035. It is therefore of considerable concern that in the UK at least, milk
72 consumption in teenage years has now reduced, particularly in females, such that considerable
73 sub-optimal intakes of calcium, iodine and other key nutrients are apparent.
74
75 Sarcopenia is an age-related progressive loss of muscle mass and strength. The meta-analysis
76 of Shafiee et al. (2017) reported that the overall prevalence of sarcopenia was 10% in males
77 and females but it was higher in non-Asian than Asian countries. There are many effects of
78 sarcopenia including reduced muscle strength and mass leading to increased risk of falls and
79 related bone breakages which can have major negative impacts on quality of life and
80 independence. It is also now appreciated that both reduced muscle mass and reduced mobility
81 can increase the risk of type 2 diabetes which further reduces healthy and quality lifespan
82 (Hunter et al., 2019).
83
84 In middle and later life cardiovascular diseases (CVD) remain a major cause of death and
85 morbidity in the EU and worldwide even though prevention and treatment programs have
86 brought major benefits (Wilkins et al., 2017). While CVD related mortality has declined in
87 most of Europe, there remain some 49 million people living with CVD in the EU which
88 represents a major healthcare cost (Wilkins et al., 2017). Of related concern is the substantial
89 rise in the prevalence of type 2 diabetes related in good part to increased obesity. Recent data
90 from Diabetes UK (2019) indicate that about 10% of people over 40 years of age now
91 have type 2 diabetes with some 4.7 million cases of all types of diabetes (~90% type 2).
92 It is predicted that by 2030 the number of cases will have reached 5.5 million.
93
94 Diet is a key risk modifying factor for chronic diseases and this must be used appropriately
95 throughout the various life stages, not least because reducing risk in early life can have benefits

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96 in later life. The intention of this review to focus on key life stage issues where milk/dairy
97 components can play a substantial role in reducing chronic disease risk. This predominantly
98 relates to high income countries although some reference is made to low income countries
99 where relevant.
100
101 **MILK IN CHILDHOOD**
102 ***Milk and growth***
103
104 The benefits of milk in a child's diets have been known for many years. For example in 1926,
105 a report produced by the UK Medical Research Council showed that giving an additional 568
106 mL/day (d) of milk to boys in a children's residential home led to a marked increase in growth
107 (Corry Mann, 1926). Subsequently, UK nutrition policy encouraged milk drinking for children.
108 In recent years there has been an increased focus on the importance of nutrition during
109 childhood as there is increasing evidence that diets during this period can influence health in
110 later life. It is well recognized that undernutrition in childhood can lead to a marked reduction
111 in linear growth (stunting), increased risk of slower short-term cognitive development and in
112 adulthood of hyperglycemia, hypertension, elevated blood lipids and obesity (de Onis and
113 Branca, 2016). Despite recent worldwide improvements, Semali et al. (2015) noted that
114 stunting in sub-Saharan African children remains at about 40 % and some countries have an
115 even higher prevalence. Recently, Leroy and Frongillo (2019) confirmed that childhood
116 stunting remains a major health concern in many parts of the world. They also proposed that
117 the conventional focus on linear growth reduction and stunting is not always the most cost-
118 efficient way to improve the well-being of children.
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120 Nevertheless, a range of studies over a substantial time period have shown milk to be a key
121 food for reducing stunting in children. In the mid-1970s a randomized controlled trial (RCT)
122 was started to evaluate the effect of milk provision at school on child growth (Baker et al.,
123 1980). Some 600 children aged 7 and 8 years in families in South Wales, UK with 4 or more
124 children were chosen from schools in areas with a high socioeconomic deprivation. The
125 selected children were on average 2.5 cm shorter and 1.5 kg lighter than the average for the
126 area, and for height, they were representative of the lowest 20% of children throughout the
127 whole region. The children in the treatment group were given 190 mL of milk every school
128 day. After 2 school years, these children were significantly taller and heavier (both $P<0.01$)
129 than those in the control group although the increases were very small (0.28 cm taller and 0.13
130 kg heavier). In addition, there was significantly increased growth in children from families in
131 the highest social classes compared with those in the lowest. More recently, Michaelsen (2013)
132 emphasized that milk has a specific growth promoting effect in children, an effect which is
133 seen in both developing and developed countries, indicating an effect even when energy and
134 nutrient intakes are apparently adequate. In a recent study in Bangladeshi children from
135 households with milk producing cows, Choudhury and Headey (2018) found that these children
136 had increased height-for-age Z scores (+0.52 standard deviations) in the crucial 6 to 23 month
137 growth phase compared with control children from households with non-milk producing
138 animals, an effect apparently not confounded by family socio-economic status. However, it
139 was also found that children aged 0–11 months from treatment households were 21.7% less
140 likely to be breastfed than children from control households, suggesting that ready access to
141 dairy milk substantially reduces the incentive for mothers to breastfeed. Reduced availability
142 of breast milk will be a considerable disadvantage for the very young child with the increased
143 acute risk of gastrointestinal infections and infant morbidity and mortality.
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145 The effect of milk on linear growth is now thought to be primarily mediated through the
146 stimulation of IGF-1 by milk proteins, in particular by casein (Hoppe et al., 2009). IGF-1 is
147 essential for longitudinal bone growth, skeletal maturation, and bone mass acquisition during
148 childhood and maintenance of bone matrix in adult life (Locatelli et al., 2014), with regulation
149 of bone length associated with changes in chondrocytes of the proliferative and hypertrophic
150 zones of the growth plate (Yakar et al., 2018). It is of note that Wan et al. (2017) showed that
151 activation of peroxisome proliferator-activated receptor gamma (PPARγ) is also involved in
152 the regulation of hepatic IGF-1 secretion and gene expression in response to dietary protein,
153 thus providing a possible explanation whereby dietary protein and related amino acids
154 stimulate hepatic secretion of IGF-1.
155
156 ***Milk, obesity and future health***
157
158 The general rise in childhood obesity in many parts of the world is a major concern. At least
159 60% of children that are overweight before puberty will remain overweight in early adulthood
160 (Nittari et al., 2019) with the increased risk of CVD (Steinberger et al., 2016) and type 2
161 diabetes. It is therefore of considerable interest that dairy consumption is inversely and
162 longitudinally associated with childhood obesity and overweight (Lu et al., 2016; Dougkas et
163 al., 2019). There are concerns however, about the so-called 'early protein hypothesis' with
164 consistent evidence that the use of infant formulae with higher protein contents than human
165 milk throughout the first year of life leads to greater abdominal fat mass in children from 2 to
166 6 years old. This is likely to be related to higher circulating IGF-1 and insulin (Totzauer et al.,
167 2018). Insulin in particular is known to promote adipose tissue deposition and this is a key
168 component of the early development of insulin resistance. Thus in many Western populations
169 there may be a need to moderate the use of the high protein formula milks in early life.

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Milk and bone health

It is now recognized that sub-optimal vitamin D status in children and adults is prevalent in many parts of the world. Holick (2010) proposed this to be a pandemic of '*a forgotten hormone important for health*'. Cashman et al. (2016) confirmed that within Europe, the prevalence of vitamin D deficiency represented a major health risk which required a major public health initiative. More recently Jazayeri et al. (2018) reported that the prevalence of vitamin D deficiency in Iranian children is very high.

A 2-year intervention study with 757 Chinese females initially aged 10 years compared those who consumed on school days, 330 mL of calcium-fortified milk with or without a vitamin D_3 supplement (5 or 8 µg). 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. Milk consumption with or without added vitamin D, led to a significantly greater rate of height increase, body weight, total bone mineral mass, and bone mineral density (BMD). The subjects who also received vitamin D relative to those receiving just milk showed significantly greater increases in (size-adjusted) total-body bone mineral content (2·4 *v.* 1·2%) and BMD (5·5 *v.* 3·2%.) (Du et al., 2004).

A study in the United States of America (US) with children aged 4-8 years (Abrams et al., 2014) found that calcium intake, when not substantially deficient, was not highly related to bone mineral status and that a supplement of 25 µg/d of vitamin D in these children did not influence calcium absorption or bone mineral status. Intake of magnesium and the amount absorbed were however key predictors of BMD and bone mineral content. The authors propose

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that this study is evidence that magnesium should be more considered as an important nutrient in relation to bone development. The extent to which these findings can be extended to other populations is at present uncertain, but milk and dairy products are important sources of magnesium for children (15-25% of intake in UK; Roberts et al.,2018) and are especially important during the phase of rapid bone growth in late childhood/early adolescence. It is also of note that low serum magnesium concentrations in males aged 42-61 years were associated with increased risk of bone fracture in the Japanese Kuopio Ischemic Heart Disease prospective study (Kunutsor et al., 2017).

It has been known for a long time that low vitamin D status in children could lead to the development of rickets and consequent increased risk of osteoporosis in later life. As noted by Holick (2010), at the start of the 20th century some 80% of children in North America and Europe suffered from rickets. Subsequently the occurrence of rickets declined markedly as a result of vitamin D fortification in some countries of foods including milk, and the policy of providing cod liver oil to children, and by the late 1930s rickets was essentially eradicated. It is therefore of considerable concern that cases of rickets are again increasing in the US (Thacher et al., 2013) and worldwide (Prentice, 2013). In the UK, Goldacre et al. (2014) reported that in England, the need for hospital treatment for rickets was at the highest level seen in the last 50 years.

Many, but not all new cases of rickets are the result of sub-optimal vitamin D status with some cases implicating sub-optimal calcium intake. Milk is of course an excellent dietary source of calcium and as noted above, milk proteins, especially casein, provide an anabolic stimulus for bone development (Hoppe et al., 2009). Although milk is not a naturally rich source of vitamin D, it is an excellent medium for vitamin D fortification. Vitamin D fortification of milk has

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been a policy in the US and Canada for a long time but in Europe such a policy for liquid milk is limited to Finland although Sweden and Norway do fortify some dairy products (Itkonen et al., 2018). Itkonen et al. (2018) also concluded that countries that have a national vitamin D fortification of milk policy, dairy foods do make a substantial contribution to vitamin D intake whereas in those with no such policy or with only a few dairy foods fortified, the contribution is low. Given the evolving picture on rickets, considerably more attention should be focused on the importance of vitamin D fortification of milk. There is also concern about the increasingly popular plant-based milk alternative drinks especially when used to replace milk for young children (Scholz-Ahrens et al., 2019). Many contain very little protein, have lower micronutrient concentrations than milk (Bath et al., 2017) and there have been cases where young children have become seriously ill as a result of consuming such milk alternatives (e.g. Fourreau et al., 2013; Le Louer et al., 2014).

Hypersensitivity to milk and dairy foods

There are 2 main types of hypersensitivities (often called intolerances) relating to dairy food consumption i.e. cow's milk protein allergy (CMPA) and lactose intolerance. These are 2 very different conditions that require medical diagnosis to avoid unnecessary or inappropriate removal of cow's milk from a child's diet which is a major event that can have significant nutritional consequences.

CMPA is an adverse immune response to proteins in cow's milk with β-lactoglobulin and αs1-casein (both absent in human milk) often being quoted as the 2 key allergenic proteins (Pastuszka et al., 2016) although many other milk proteins can be involved. CMPA is usually recognized as 2 sub-types, the IgE-mediated rapid onset and non-IgE-mediated delayed onset

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variants (Vojdani et al., 2018) with anaphylaxis and related death being possible in severe cases of the rapid onset sub-type (Turner et al., 2015). CMPA is the most common type of food allergy and usually affects very young children although a high proportion are in remission by the age of 3 years (Host and Halken, 2014). The increased prevalence of CMPA has been suggested to be the result of increased use of cow's milk as a substitute for human milk (Rangel et al., 2016) although the recent study of Munblit et al. (2020) reports that identification and management of symptoms as CMPA is often not evidence-based suggesting that there may be considerable over-diagnosis.

Lactose intolerance is a non-allergic hypersensitivity that results from a reduced ability to digest lactose. Intestinal digestion and absorption of lactose requires the enzyme lactase and deficiency or insufficiency of lactase leads to malabsorption of lactose and subsequent digestive upset. The ability or otherwise to synthesize lactase is genetically determined. For a full and up to date review of lactose intolerance and CPMA the reader is referred to Miles (2020).

MILK IN ADOLESCENCE

Adolescence and dietary change

Adolescence is the life period (10-19 years, WHO, 1999) involving hormonal changes, rapid growth and sexual maturation. There are also changing dietary habits, new motivations and challenges, some persisting into adulthood (Forbes and Dahl, 2010). The age of puberty onset has reduced substantially over the last 100 years; currently the UK average age for males and females is 12 and 11 years respectively (NHS, 2019).

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In the UK, data from the National Diet and Nutrition Survey covering the period 2008/09-2011/12 (Bates et al., 2014) identify that adolescent females in particular, have considerably lower milk consumption than those under 11 years of age while older age groups have somewhat higher intakes (Figure 1). A similar picture has been seen in the more recent National Diet and Nutrition Survey covering a longer period 2014/15 to 2015/16 (Roberts et al., 2018) and this will have contributed substantially to the lower intakes of some key nutrients by adolescent females (Table 1).

The reasons for the lower intakes of milk by adolescent females are not known with certainty. However, poor complexion or weight gain during adolescence is often attributed to milk consumption. The recent large meta-analysis of RCT on the association between milk/dairy consumption and body composition in children and adolescents (n=2844; 6-18 years old) does not support the fattening belief, the primary finding being that consumption of milk/dairy foods is more likely to produce a lean body phenotype (Kang et al., 2019).

The very low intakes of magnesium by UK adolescent females are worrying given the evidence concerning the possible key association between magnesium status and bone mineral status (Abrams et al., 2014; Kunutsor et al., 2017) summarized above. Larson et al. (2009) noted that US National Survey longitudinal data suggest that only 53% of young males and 21% of young females (19 to 30 years) have calcium intakes that meet recommendations. They also showed that in the Eating Among Teens (EAT) study both male and female adolescents recorded significant reductions in calcium intake and dairy food (main reduction was in milk) consumption from baseline (mean age of 15.9 years) to early adulthood (mean age 20.5 years). The mean daily reduction in calcium intake was 153 mg and 194 mg for females and males respectively (both about -15%). It was also seen that greater availability of milk at mealtimes,

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a liking for milk and peer support for healthy eating at baseline were associated with smaller reductions in calcium intake (Larson et al., 2009). Given the coexistence of suboptimal vitamin D status, the above data give rise to considerable concern.

Milk and bonetrophic nutrients

The US National Osteoporosis Foundation's position paper concerning peak bone mass development (Weaver et al., 2016) emphasized that bone mineral accretion rate becomes rapid around the time of puberty and reaches its peak a little after achieving maximum height gain. Weaver et al. (2016) indicated 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 males. They emphasized that sub-optimal bone mineral accretion in teenage years increases the risk of osteoporotic fractures in later life, particularly for post-menopausal females. This is supported by the study of Black et al. (2002) which found that male and female New Zealand children with a long history of avoiding milk had poor bone health with small bones, low areal BMD and volumetric bone mineral apparent density, and a high prevalence of bone fractures. Also, Kalkwarf et al. (2003) used data from 3251 white females in the US National Health and Nutrition Examination Survey and reported that milk consumption in childhood and adolescence was positively associated with bone mass in later life and negatively associated with osteoporotic fracture after 50 years of age. It is of interest that the association between milk intake in childhood and fracture rate was higher than for milk consumption during the period of adolescence. This issue was also raised by Feskanich et al. (2014) who, in an analysis of post-menopausal females in the Nurses' Health Study, found no association between hip fractures and milk consumption in teenage years. They queried whether data for milk consumption during pre-teenage years would have been more helpful since females reach

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maximum height about 2 years sooner than males and are younger at the start of puberty when bone mineralization doubles (Feskanich et al., 2014). There must also be a question about the quality of recall of diet data from adulthood back to adolescence and childhood.

More recently the study by Ma et al. (2014) reported that in Chinese adolescents (12-14 years of age), females in the high-calcium intake group (mean 1243 mg/d) had greater increases in BMD of the femoral neck relative to those in the low-calcium intake group (mean 706 mg/d) over the 12 month intervention period. A similar effect was observed in males. They proposed that to increase bone mineral mass, calcium supplementation is more effective in early than late puberty and that additionally, children should be encouraged to increase their weight-bearing exercise which enhances the effect of dietary calcium.

The strength of evidence for effects of milk/bonetrophic nutrients on bone development in adolescents is fairly strong but there remains more uncertainty about the effect on bone health in middle and later life following long term exposure to diets low or devoid of milk/dairy. Also, a recent systematic review and meta-analysis of the associations between vegan and vegetarian diets and bone health gives further evidence on the chronic effect of diets containing low or zero milk and dairy products (Iguacel et al., 2018). Twenty studies of adequate quality were included in the meta-analysis of Iguacel et al. (2018) which included 37,134 participants of which 33,131 had data on fracture rate and 4003 data on BMD. Overall, compared with omnivores, vegetarians and vegans had significantly lower BMD at the femoral neck, lumbar spine and whole body, with vegans generally exhibiting lower BMD than vegetarians (Table 2). Vegans also had a higher relative risk (RR) for fracture rate (RR: 1.44; 95% confidence interval (CI) 1.047-1.977) particularly in subjects aged over 50 years. These findings highlight

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345 the absolute need for careful, detailed and long-term planning of vegetarian and vegan diets in
346 order reduce the risk of negative effects on bone health.
347
348 A very recent review on milk and bone health (Batty and Bionaz, 2019) has provided some
349 new thinking on the mechanisms concerning the role of milk in bone development including
350 the possible role of micro-RNA (miRNA) contained in milk. While there appears to be
351 considerable, but building evidence that endogenous miRNA is involved in regulation of
352 osteoblastic differentiation and other pathways relevant to bone development in adolescents,
353 there remains uncertainly about the effect of miRNA provided by the diet in the form of
354 exosomes. Zempleni (2017) has shown that exosomes are absorbed and can accumulate in
355 peripheral tissues but the functionality of their miRNA is unclear. At present the possible
356 involvement of milk-derived exosomes/miRNA in bone development and maintenance
357 remains speculative and is clearly a target for further research.
358
359 **MILK AND PREGNANCY**
360
361 ***Iodine status during pregnancy***
362
363 In the UK and many other countries milk and milk products are the biggest dietary source of
364 iodine by a considerable margin. The recent UK National Diet and Nutrition Survey (Year 8,
365 20114/15-15/16; Roberts et al., 2018) reports that milk and milk products contribute 40% and
366 34% of dietary iodine intake for 11-18 years and 19-64 years age groups respectively, with
367 liquid milk being the primary dairy source. Fish are the next largest contributor to dietary intake
368 at 10% for both age groups. Interestingly, milk and dairy products were also shown to be the

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most important determinant of iodine status in US adult (≥ 20 years) males and females, despite the availability of iodized salt (Lee et al., 2016).

Until fairly recently it was believed that the UK population was of adequate iodine status. However, a study which measured iodine concentrations of urine from UK schoolgirls showed 51% of them to be mildly iodine deficient (Vanderpump et al., 2011). As noted earlier, 27% of adolescent females (11-18 years) have iodine intakes below the Lower Reference Nutrient Intake (70 µg/d), while the mean value for females 19-64 years is 15% (Roberts et al., 2018; Table 1) but given the milk intake values in Figure 1, females of childbearing age are likely to exceed this value substantially. Of particular concern are the results from a study in a large UK cohort of pregnant females which showed consistent mild-to-moderate iodine deficiency (Bath et al., 2014) with similar findings in pregnant Norwegian females (Brantsæter et al., 2013). Bath and Rayman (2015) reviewed the then current evidence on the iodine status of pregnant females in the UK and the risks to child development after birth (as discussed below) associated with below optimum status. They concluded that a substantial proportion of UK pregnant and non-pregnant women were iodine deficient. The WHO database on iodine deficiency (WHO, 2020) highlights that large parts of the world are affected with substantial parts of Africa and Asia having mild or moderate deficiency. Example studies include one from Tanzania that reported an unacceptably high prevalence of iodine deficiency among pregnant females (Abdalla et al., 2017) and a recent assessment on the iodine status of teenage females on the island of Ireland (Mullan et al., 2019) showed that this population were at 'the low end of sufficiency' which clearly has implications for their future progression into pregnancy and for child development after birth (as discussed below).

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Bath and Rayman (2015) also discussed the potentially contributing fact that UK recommendation for iodine intake of 140µg/d for adults (Department of Health, 1991) is not only lower than WHO et al. (2007) recommends for non-pregnant/non-lactating adults and adolescents (>12 years of age) (150µg/d) but it does not increase during pregnancy (or lactation) whereas WHO et al. (2007) recommends an increase to 250µg/d. There are clear needs for a greater iodine intake during pregnancy including the demands associated with substantially increased maternal thyroid hormone production in early pregnancy and later for the fetus when it is able to synthesize thyroid hormones (Bath and Rayman, 2015).

It is concerning to note that that there are now a number of studies from several countries including Spain (Costeira et al., 2011), The Netherlands (van Mil et al., 2012), Australia (Hynes et al., 2013) and the UK (Bath et al., 2013) that have found a significant association between low maternal iodine status in early pregnancy and poorer cognitive performance/neurological development in the children. A systematic review and meta-analysis found that low maternal iodine status was associated with 6.9 to 10.2 lower IQ points in children <5 years of age (Bougma et al., 2013). They concluded that independent of study type, low iodine status had a major effect on mental development. It is also worth recording that Businge et al. (2019) reported that although sub-clinical hypothyroidism during pregnancy is one of the key risk factors for pre-eclampsia, the connection between sub-optimal iodine status and pre-eclampsia remains uncertain. Given the risks associated with pre-eclampsia, Businge et al. (2019) proposed that a systematic review and meta-analysis on the subject should be undertaken.

Given the potentially serious implications of sub-optimal iodine status on child development, there is a clear need for more precise RCT to give more definitive evidence on the need for supplementary iodine during pregnancy to avoid impaired neurological development of the

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offspring. Such studies would no doubt raise important ethical considerations, but it is interesting to note that in the study of Bath et al. (2014), only females consuming more than 280 ml of milk/d had achieved adequate iodine status and a recent RCT in low-moderate (<250 mL/d) milk consuming females showed that increasing consumption to 459 mL/d (3L/week) of semi-skimmed (fat reduced) milk significantly increased their iodine status (O'Kane et al., 2018). The volume of milk needed to achieve an adequate iodine intake will clearly depend on its iodine concentration which can be substantially variable.

Factors affecting the iodine concentration in milk

Survey studies on UK milk iodine concentrations (Food Standards Agency, 2008) do not suggest that 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, 4 UK studies (Food Standards Agency, 2008; Bath et al., 2012; Payling et al., 2015; Stevenson et al., 2018) and the meta-analysis of Średnicka-Tober et al. (2016) all reported that milk from organic dairy systems had significantly lower iodine concentrations than from conventional systems. The interacting involvement of season and production system on milk iodine concentration can be seen in Figure 2 from Stevenson et al. (2018). The review of Flachowsky et al. (2014) confirms that the iodine intake by the dairy cow has the primary influence on milk iodine concentration. Since most iodine is provided to the cow by concentrate feeds, this would explain the lower values reported in milk in the summer and from organic systems, since the animals in both situations are likely to be provided with less concentrate feeds. The effect of iodine supplements (30 or 70 mg/d) to dairy cows were compared to a control (0 mg/d). Iodine concentration increased ~2 fold in the milk of the supplemented animals compared with the non-supplemented animals. No difference was seen between the 30 and 70 mg/d doses

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(O'Brien et al., 2013). It is important to note that the iodine concentrations in milk from the iodine-supplemented diets were much higher (up to 1034 µg/kg) than is desirable for processing into infant formula products. As the authors point out, the supplemented diets did not contain more iodine than the maximum prescribed in the present EU legislation (5 mg iodine/kg diet at 12% moisture; European Commission, 2005). O'Brien et al. (2013) also showed that the use of iodine-containing teat disinfection products both pre- and post-milking increased milk iodine concentration ($P < 0.001$**)** at all of the dietary iodine supplementation amounts. This and a number of additional factors which influence milk iodine concentration are extensively reviewed by Flachowsky et al. (2014).

Overall, knowledge on the relationship between iodine in the dairy cow diet and milk iodine concentration, together with other factors, provides a means to produce milk with the required iodine concentration for consumption by adults but avoiding concentrations too high for children.

MILK IN ADULTHOOD

Milk consumption and body composition

The prevalence of overweight and obesity (body mass index (BMI) of 30 kg/m^2 or more) continues to rise worldwide. OECD (2017) reports that since the 1990s overweight and obesity rates have increased substantially in England, Mexico and the US although the increase has been somewhat slower in the other 7 OECD countries for which data are available. It was also noted that in 2015, 19.5% of adults in OECD countries were obese but this was highly variable

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467 with for example <6% in Korea and Japan but up to >30% in Hungary, New Zealand, Mexico
468 and the US.
469
470 Obesity is a major risk factor for chronic diseases, particularly diabetes, CVD, stroke and some
471 cancers. The association between obesity/overweight and type 2 diabetes is particularly critical,
472 accounting for up to some 70-90% of the risk for type 2 diabetes (Hu et al., 2001; Gatineau et
473 al., 2014), although there remains some uncertainty why some obese subjects do not develop
474 type 2 diabetes (Abdullah et al., 2010).
475
476 It is not the intention of this paper to review in detail all the evidence on the association between
477 milk/dairy and obesity. There is however, a large amount of evidence from observational,
478 cross-sectional, and prospective studies which is consistent with a negative association between
479 dairy consumption and both body weight and central obesity (Dougkas et al., 2011). The review
480 of Kratz et al. (2013), using observational and RCT evidence, found that in 11 out of 16 studies,
481 high-fat dairy consumption was inversely associated with measures of adiposity whereas the
482 association between high-fat dairy and metabolic health was either inverse or had no
483 association. The recent report on middle-aged males (at baseline) in the Caerphilly Prospective
484 Cohort showed no association between milk consumption and BMI, but higher cheese
485 consumption was associated with lower BMI at the 5-year follow-up (P=0.013) (Guo et al.,
486 2018).
487
488 Many RCT have evaluated the association between dairy consumption and body weight and
489 fat mass, but the majority have been small and of limited duration and although some have
490 included energy restriction, others have focused on weight maintenance with the overall
491 findings being difficult to interpret. Nevertheless, a meta-analysis of 29 RCT of varied designs

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showed that while the inclusion of dairy foods in weight maintenance diets is not associated with weight loss or weight gain, there were weight loss benefits from the combination of these foods and energy-restricted diets (Chen et al., 2012).

Milk consumption, stroke, cardiovascular and metabolic diseases

It is interesting to note that while in most high income countries the prevalence of death from CVD has reduced considerably over recent decades, it is concerning that recent data from the US indicate a levelling off of the decline, thought probably a result of increasing obesity and related type 2 diabetes (Zia et al., 2018). These data highlight the risk of complacency and the continued need for the management of lifestyle including diet. In this regard and as noted above, the impact of dairy foods in the diet is poorly understood by many in the general population.

Evidence from prospective studies. Many prospective studies have investigated the association between milk and dairy product consumption and cardiometabolic diseases (CMD, includes CVD, stroke and type 2 diabetes). Data from prospective cohort studies are usually regarded as providing poorer evidence than that from RCT since they only estimate risk and cannot prove cause and effect, but they do have the advantage of looking at chronic effects and use hard disease data outcomes. Another limitation of this type of study is the presence of variables (confounders) which are beyond the control of the researchers (e.g. some subjects may be smokers, some will not) but which can influence the variables being studied (e.g. the effect of cheese consumption on the risk of CVD) leading to results which do not represent the actual association. This is normally dealt with by including the confounder in the statistical model used so that as far as is possible its effect is removed, however there often remains some

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residual confounding not accounted for. Long-term RCT using hard disease endpoints would be impractical, very costly and likely with high subject dropout rates with the result that most RCT are relatively short term and use markers of disease risk such as low density lipoprotein cholesterol (LDL-C) as primary outcome measures. Meta-analysis of prospective data is a valuable tool for investigating the overall associations between dairy food consumption and CMD risk, although there is a concern that in many studies these foods are poorly defined, especially their fat content, which limits assessment of any differential effects.

While there have been several other meta-analyses published over recent times, a series of dose-response meta-analyses was published in 2016/17 examining the 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). The availability of new data has allowed key components of these meta-analyses to be updated (Soedamah-Muthu and de Goede, 2018) and the outline results are presented in Table 3.

Overall, these prospective studies show no increase in risk of coronary heart disease (CHD) and stroke per 200g increase in total dairy and milk. Interestingly, milk and yogurt consumption was associated with a substantially reduced risk of stroke and type 2 diabetes respectively. The reduced risk of type 2 diabetes associated with yogurt consumption is also highlighted in the recent review of evidence of Guo et al. (2019). There are few studies which have looked into the association between butter consumption and CMD although the dose-response meta-analysis of Pimpin et al. (2016) showed no significant association between butter consumption and all-cause mortality, CVD, CHD specifically, or stroke, although there was a significant negative association with type 2 diabetes. This meta-analysis involved only a few cohorts for CVD (*n*=4), CHD (*n*=3), stroke (*n*=3) although 11 cohorts were judged to be suitable for

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inclusion for type 2 diabetes. More recently, Griffin and Lovegrove (2018) raised the possibility that increased high density lipoprotein-mediated cholesterol efflux capacity compensates for the adverse effect of saturated fatty acids (SFA) in butter in raising blood LDL-C.

The Prospective Urban Rural Epidemiology (PURE) study recently published its results (Dehghan et al., 2018). PURE is a multinational cohort study of 136,384 subjects aged 35-70 years from 21 countries (6, 11, 4 low, middle and high income respectively) across 5 continents, which examined the association between consumption of dairy foods (total and milk, yogurt, and cheese) with mortality and CVD. Higher intake of total dairy foods (>2 servings/d vs. none) was associated with a lower risk of non-CVD mortality (hazard ratio (HR) 0.86, 95% CI 0.72-1.02**;** P_{trend} = 0.046), CVD mortality (HR 0.77, 95% CI 0·58-1·01; P_{trend} = 0·029), major CVD events (HR 0.78, 0.67-0.90; P_{trend} = 0·0001), and stroke (HR 0.66, 0.53-0·82; P_{trend} = 0·0003). Greater consumption of milk and yogurt, but not cheese, was associated with a lower risk of the combination of mortality or major CVD events. Although the results from PURE are largely in agreement with earlier studies and meta-analyses, it is believed to be the first study of its kind to involve such large and diverse cohorts of subjects with substantial variation in habitual dairy and other dietary component intake between regions and countries.

Overall, the findings from meta-analyses of prospective cohort studies provide no evidence of an increased risk of CMD associated with increased consumption of dairy foods despite most of these foods making a major contribution to SFA intake. These findings may seem counterintuitive in view well-established link between LDL-C and CVD. There is however emerging evidence which goes some way to explaining these relationships, including

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566 differential effects of different SFA and the food matrix influences (Thorning et al., 2017;
567 Astrup et al., 2019).
568
569 A number of prospective studies have also examined the association between milk/dairy intake
570 and blood pressure. For example, findings from the Caerphilly Prospective Study indicate that
571 after a 22.8 year follow-up, men who consumed >586 mL/d of milk had a mean lower systolic
572 blood pressure of 10.4 mmHg, compared with non-milk consumers (P_{trend} = 0.033)
573 (Livingstone et al., 2013).
574
575 ***Evidence from randomized controlled trials.*** The American Heart Association recently
576 reported that in 2015 the proportion of US adults ≥18 years of age with diagnosed hypertension
577 was 29.7% (age adjusted) although there was considerable variability with equivalent values
578 ranging from 24.2% for Minnesota to 39.9% for Mississippi (Benjamin et al., 2018). Data from
579 2016 in England indicate that 28 % of adults had diagnosed hypertension (National Statistics,
580 2017a). In addition, there are substantial numbers of individuals with undiagnosed
581 hypertension. Hypertension is one of the major risk factors for CVD and for stroke in particular.
582
583 There is now good evidence that the proteins in milk and milk derived products have beneficial
584 hypotensive effects, particularly whey proteins. This has been shown in vitro (Giromini et al.,
585 2017) and in vivo. An 8-week RCT (Fekete et al., 2016) found that whey protein isolate (2 x
586 28g/d) had a larger hypotensive effect than casein with effects seen on both central and
587 peripheral blood pressures. Whey protein was also shown to have a greater effect than casein
588 in an acute setting (Fekete et al., 2018). A number of mechanisms by which milk and its
589 components could lower blood pressure have been proposed including the effects of dairy
590 nutrients, in particular calcium, potassium and magnesium (Kris-Etherton et al., 2009), and the

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591 effect of milk protein-derived peptides (Fekete et al., 2013). A number of peptides released
592 during digestion of casein and whey proteins possess hypotensive activity through inhibiting
593 the action of the angiotensin-1-converting enzyme that would normally increase the production
594 of angiotensin-2 which has a vasoconstricting effect leading to increased blood pressure
595 (FitzGerald and Meisel, 2000; Giromini et al., 2019). Other effects of milk protein-derived
596 peptides may be important such as binding with opioid receptors thus increasing nitric oxide
597 production which mediates arterial tone and thus reduces blood pressure (Kris-Etherton et al.,
598 2009).
599
600 Recent work on hemodynamics has shown that arterial stiffness, especially of the central large
601 vessels, is a valuable predictor of future CVD events (Cockcroft and Wilkinson, 2000). Milk
602 and dairy consumption have been shown to be associated with reduced arterial stiffness.
603 Livingstone et al. (2013), working with the Caerphilly Prospective Study, showed, it is believed
604 for the first time in a longitudinal study, that augmentation index (an indirect measure of arterial
605 stiffness) was 1.9% lower in subjects with the highest dairy product consumption (not including
606 butter) compared with the lowest (P_{trend} = 0.021) after a mean follow up period of 22.8 years.
607 A similar effect was seen in a cross-sectional study that showed a negative association between
608 milk/dairy consumption and pulse wave velocity (another indirect measure of arterial stiffness,
609 Crichton et al., 2012). More recently, the specific effect of milk proteins together with exercise
610 has been shown to reduce arterial stiffness in pre-hypertensive and hypertensive young females
611 (Figueroa et al., 2014). Whey protein and casein both significantly ($P < 0.05$) reduced arterial
612 stiffness as indicated by reduced augmentation index by about 9.2% and 8.1%, respectively
613 and reduced pulse wave velocity by 57 cm/s and 53 cm/s, respectively compared with no
614 changes in the control group.
615

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Food matrix effects of dairy products on blood lipids. New evidence on the food matrix goes a considerable way to explaining the lack of effect of dairy SFA on CVD risk. This topic has been extensively discussed recently by Astrup et al. (2019) and will not be fully repeated here, but aspects of food matrix effects are worthy of mention.

Traditionally, nutritional evaluation of foods and diets and their links with the health/disease of the consumer has normally been assessed on separate considerations of food components, notably protein, fat, carbohydrates and micronutrients. For some dairy foods there is now good evidence that this approach is not appropriate and indeed may mislead since the modifying effects of the so-called food matrix needs to be considered. This subject was extensively reviewed by an expert working party jointly established by the Universities of Copenhagen and Reading and the outcome has been published (Thorning et al., 2017).

A good illustration of the differential matrix effects on blood lipids of SFA from hard cheese and butter is reported in the RCT of Hjerpsted et al. (2011). This involved two 6-week crossover periods with 49 males and females replacing part of their habitual dietary fat with 13% of energy from cheese or butter (both providing 80 g/d and 36 g/d of total fat and SFA, respectively). Crucially, the cheese and butter diets provided 1192 g and 417 g of calcium/d, respectively. Compared with baseline, cheese did not increase blood total cholesterol or LDL-C whereas the butter diet increased both of these ($P<0.001$, 0.05 respectively). The cheese diet led to a 5.7 and 6.9 % lower total cholesterol or LDL-C concentrations respectively, than the butter diet ($P< 0.0001$). The recently published and rather unique study of Feeney et al. (2018) attempted to explore the matrix effect in a stepwise-response fashion. The study was a 6-week randomized parallel design where subjects consumed 40 g of dairy fat/d in macronutrient-matched food matrices as either 1) 120 g full-fat cheddar cheese, 2) 120 g reduced-fat cheddar

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641 cheese plus 31 g of butter, or 3) 49 g butter plus 30 g calcium caseinate and 500 mg of calcium
642 as $CaCO_3$. The blood lipid responses are summarized in Table 4 but the results did indeed
643 show a stepwise-matrix effect with significantly lower post-intervention total cholesterol and
644 LDL-C concentrations seen when all of the dairy fat was provided by the cheese.
645
646 Several mechanisms have been proposed as being responsible for the benefits of the so-called
647 matrix effect and these are reviewed in detail by Thorning et al. (2017). In brief, most studies
648 involving hard cheese result in increased fecal fat and calcium excretion which, in part at least,
649 seems to be the result of a saponification reaction in the gut between calcium and fatty acids
650 leading to largely indigestible soaps. There is also evidence that fecal bile acid excretion is
651 increased due to adsorption on amorphous calcium phosphate formed from dietary calcium and
652 phosphorus. This reduces the enterohepatic recycling of bile acids thus increasing bile acid and
653 fat excretion. Since the liver synthesizes bile acids from cholesterol, reduced bile acid recycling
654 may also lead to reduced circulating cholesterol. There is also evidence of a role for the milk
655 fat globule membrane apparently protecting fat from digestion. A good example of this is in
656 the study of Rosqvist et al. (2015).
657
658 These studies clearly confirm that the effect of dairy foods on CVD risk factors, primarily blood
659 lipids, are influenced by the food matrix, even when compared with foods providing the same
660 amount of dairy fat and SFA. However, most of the evidence available relates to hard cheese
661 vs. butter and as proposed by Thorning et al. (2017), more research is required to more fully
662 understand food matrix effects on health and how these relate to specific dairy foods and
663 methods of processing and cooking.

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MILK AND DAIRY PRODUCTS FOR THE ELDERLY

Dairy proteins and sarcopenia

Sarcopenia: the condition. Sarcopenia is a condition characterized by a mainly chronic ongoing loss of muscle mass and muscle strength with advancing age (Cruz-Jentoft et al., 2019). It is therefore a condition of particular importance in the elderly (though not exclusively) with an increasing prevalence mainly associated with the increasing age of populations worldwide. Sarcopenia can have far reaching consequences since, for example, it reduces bone protection increasing the risk of breakage in a fall leading to reduced mobility, disability and lower quality of life. A less well known outcome of reduced muscle mass and possibly associated reduced exercise ability is the increased risk of metabolic diseases, type 2 diabetes in particular (Hunter et al., 2019).

Based on general population studies, Shafiee et al. (2017) published a meta-analysis on the prevalence of sarcopenia worldwide involving a total 58,404 generally healthy subjects >60 years of age. This study showed a mean prevalence of 10% in both males and females, with a higher value in non-Asian than Asian populations with the non-Asian values (~20%) being about double those of Asians when Bio-electrical Impedance Analysis was used to estimate muscle mass.

The role of dietary proteins for reducing sarcopenia. Consumption of protein and resistance exercise are both known to provide an anabolic stimulus for skeletal muscle protein synthesis and there has been considerable debate about the amounts and the relative timing of protein

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consumption and exercise needed to stimulate muscle protein synthesis in the elderly. In the UK, the Reference Nutrient Intake for protein is equivalent to 0.75g/kg body weight, slightly less than the Recommended Dietary Allowance (RDA) of 0.8 g/kg body weight proposed for males and non-pregnant and non-lactating females >18 years of age by the FAO/WHO/UNU (2007). These recommendations take no account of specific age or health status and Lonnie et al. (2018) have discussed and highlighted the relevance of new recommendations suggesting protein requirements of 1.0-1.2, 1.2-1.5 and 2.0 g/kg body weight respectively for people >65 years, for those with acute/chronic illnesses and those with severe illness or malnutrition respectively. The review of Lonnie et al. (2018) cites work which confirms that intake of protein in accordance with the RDA has led to deleterious health outcomes including a 14-week RCT in subjects aged between 55 and 77 years who consumed the FAO/WHO/UNU RDA of 0.8 g protein/kg bodyweight which led to a reduced mid-thigh muscle area and other characteristics suggesting the protein intake was below requirement (Campbell et al., 2001). This is concerning since in the UK the latest National Diet and Nutrition Survey (Roberts et al., 2108) indicates a mean protein intake of 75.8 g/d (males) and 60.5 g/d (females) 65+ years old, which with a mean bodyweights for this age group of 85.8 kg (males) and 71.5 kg (females) (National Statistics, 2017b), equates to 0.88 and 0.85 g protein/kg bodyweight for males and females respectively.

Overall, there is considerable agreement of the benefits from increasing protein intake to 1.0 g/kg body weight or higher by the elderly, yet there have been concerns that the strong satiating effect of protein may limit total food and energy intake. In addition there have been concerns that higher protein intake may adversely affect individuals with chronic kidney disease which may be undiagnosed. The meta-analysis of Devries et al. (2018a) compared the effect of low (mean 0.93g/kg body weight per day) vs high (mean 1.81 g/kg body weight per day) protein

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714 diets and showed no effect on kidney function in subjects with normal function and in those
715 with type 2 diabetes who would have a greater risk of chronic kidney disease. Nevertheless, it
716 is probably wise for the elderly to have regular tests of kidney function irrespective of diet.
717
718 ***Type of dietary proteins for reducing sarcopenia.*** There has been considerable research on the
719 relative anabolic effects of specific protein types. Wall et al. (2014) concluded that proteins
720 such a whey protein which are rapidly digested and absorbed lead to greater muscle protein
721 synthesis than from slower digested proteins like casein and those in soya. They also note that
722 even when casein is hydrolyzed to increase digestion rate, the muscle protein response is still
723 smaller than from equivalent amounts of whey protein. This is primarily attributed to the higher
724 leucine content of whey protein, the specific effect of leucine having also been seen in studies
725 using leucine supplements (Wall et al., 2013; Devries et al., 2018b). The effect of leucine is
726 complex. It is an important activator of the mammalian target of rapamycin (mTOR) a nutrient-
727 sensing signaling pathway in skeletal muscle. In addition, leucine is insulinotrophic and the
728 additional insulin enhances muscle protein synthesis (Paddon-Jones and Rasmussen, 2009).
729 There is evidence however, that consumption of 40g of casein before sleep increases muscle
730 protein synthesis rates during overnight sleep in older males (Kouw et al., 2017). This is
731 potentially important as overnight is generally a period of negative whole body protein net
732 balance.
733
734 A number of studies have compared the relative value of plant proteins compared with whey
735 protein. The study of Yang et al. (2012) compared the response in myofibrillar protein
736 fractional synthetic rate (FSR) in rested elderly males resulting from 0, 20 or 40g of either
737 whey protein or soya protein. Myofibrillar FSR did not respond to consumption of 40g soya
738 protein compared with 20g, but it responded essentially in a linear fashion to increased whey

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protein. A similar differential effect was seen when the protein supplements were given post-exercise.

Magnesium and sarcopenia. As with the influence of magnesium intake on bone mineralization noted earlier, there is also increasing evidence of an association between magnesium and preservation of skeletal muscle. With a large cohort of 156,575 males and females aged 39-72 years, Welch et al. (2017) examined cross-sectional associations between magnesium intake and skeletal muscle mass (as fat-free mass % body mass (FFM%)) and grip strength. They showed positive associations between quintiles of magnesium intake and FFM% (P trend < 0.001) and grip strength (P trend <0.001). The association with grip strength was greater in older (60 years of age or older) than younger males although the opposite was the case for females.

Despite being a cross-sectional study, it was, according to the authors, the largest population to date used to study the association between magnesium intake and direct measures of skeletal muscle. Milk and milk products are important sources of magnesium contributing some 13% to diets of the elderly (Roberts et al., 2018) and in the US it was reported that consuming the recommended quantities of dairy would significantly reduce the prevalence of low magnesium intake (Quann et al., 2015). Erem et al. (2019) highlighted that magnesium intake is particularly low in the elderly US population which is similar to the UK where 25% of individuals 75 years old and above consume less than the Lower Reference Nutrient Intake. Clearly more work on this is needed but this study adds to increasing importance of magnesium in muscle and bone health.

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Dairy foods and bone fragility

Type of dairy foods. Unlike the situation with the young, the effect of dairy foods on bone strength in the elderly is less clear. A meta-analysis of 6 cohorts reported a 17% increased risk of hip fracture in males and females who consumed less than 1 glass of milk per day although the change was not significant (Kanis et al., 2005) and a later meta-analysis including a further 6 cohorts found no association between milk consumption and hip fracture risk (Bischoff-Ferrari et al., 2011). More recently, data from the Framingham Original Cohort (mean age at baseline 75 years) showed that higher milk and milk+yogurt+cheese intakes were associated with higher lumber spine BMD (P=0.011, 0.005) and higher milk+yogurt+cheese intakes protected against trochanter BMD loss (P=0.009) over 4 years. In all cases, the significant beneficial associations were only seen in subjects that were vitamin D supplement users (Sahni et al., 2014). The results from a Swedish female cohort indicated a significant 9% increased risk of hip fracture per glass of milk per day while no effect was seen in a male cohort (Michaëlsson et al., 2014). The reasons for the positive associations in the females are unclear.

More recently, the analysis of 2 US cohorts containing 80,600 post-menopausal females and 43,306 males greater than 50 years of age at baseline that were followed up for 32 years reported that for females and males combined, each serving of milk/d was associated with a 8% lower risk of hip fracture (RR 0.92, 95% CI 0.87-0·97) compared with those that consumed less than 1 serving per week (Feskanich et al., 2018). The authors suggested that a major strength of the study was that multiple measures of milk and dairy food intake were made over the 32 years of follow-up allowing long term mean intakes to be estimated. Calcium, vitamin D and protein from non-dairy and dairy sources did not influence the association between milk and fracture risk in this study although a recent meta-analysis of 20 studies showed that a

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788 dietary pattern classified as ‘milk/dairy’ led to the greatest reduction in risk of low BMD
789 compared with patterns classified as ‘healthy’ and ‘meat/Western’ and the effect remained
790 significant in older females (Fabiani et al., 2019).
791
792 Ong et al. (2019) conducted a systematic review on fermented milk products (yogurt and
793 cheese) and bone health in post-menopausal women. The analysis included RCT, prospective
794 cohorts and case-control studies. Overall, only increased yogurt consumption was associated
795 with a reduced risk of hip fracture when compared with little or no intake. The evidence for
796 cheese was limited and suggests that further work to understand the effect of yogurt is needed.
797
798 ***Magnesium and bone health.*** The possibly important role of dietary magnesium for bone
799 development in young people was discussed earlier but there is now some evidence of a similar
800 benefit in later life. The review of Erem et al. (2019) highlights that the risk of osteoporosis in
801 older people can result from low intake of magnesium which gives rise to excess calcium
802 release from bone and increased excretion which increases bone fragility and hence a higher
803 risk of bone fractures. Also, high intakes of calcium can lead to lower retention of magnesium
804 and Erem et al. (2019) suggest that the optimal dietary ratio of calcium:magnesium is between
805 2.0:1.0 and 2.8:1.0 but in many current US diets the ratio above 3.0:1.0.
806
807 There is an obvious need to further explore the role of magnesium and its interaction with
808 calcium and vitamin D in relation to bone strength in the elderly. Dairy products are a good
809 source of calcium and for many an important source of magnesium along with vitamin D when
810 fortification is practiced.
811
812 **CONCLUSIONS**

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Despite a favorable ongoing increase in life expectancy, an increase in healthy lifespan is not assured and indeed some of the health issues in aging populations arise because of longer life. Moreover, there is now increasing evidence that diets in early life can influence health in older life stages. There is good evidence that milk and dairy foods are important sources of nutrients some of which are particularly important at certain life stages. The concentration of some nutrients, notably iodine, are also dependent in the diet of the milk producing animal, a good example of an early stage in the food chain having an influence on nutrient intake. The reduced milk consumption, notably by adolescence females, is a major worry since it may have already had an impact on bone development such that reduced bone strength may become evident when they are much older. Despite being counterintuitive to many, there is now consistent evidence that consumption of milk/dairy foods does not increase the risk of CMD, indeed a number of significant negative associations with risk of this group of diseases have been reported. The negative and positive associations of yogurt with type 2 diabetes and bone strength respectively are particularly interesting given the rapid rise in prevalence of type 2 diabetes and bone weakness and these should be researched with urgency to identify the mechanisms involved and to develop yogurt with targeted efficacy. Much greater effort is also needed to reduce malnutrition in the elderly and to reduce the loss of muscle mass, bone strength and functionality and this seems to provide good opportunities for dairy products to play a key role. There is of course an ongoing debate about the relative sustainability of animal vs. plant food sources. While it makes sense to examine this tradeoff, it is important that judgements on the replacement of dairy products with those from plants include evidence on relative functionality (e.g. hypotensive and muscle protein synthesis stimulation effects) and not only on simple comparisons of nutrient content (Grant and Hicks, 2018). Interestingly, a very recent, detailed modelling of the relationship between diet and health care costs concludes that adoption of a

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dietary pattern with increased dairy consumption by US adults would have the potential to save billions of dollars (Scrafford et al., 2020).

ACKNOWLEDGMENTS

This paper is based on an invited contribution to the symposium on 'Improving Milk Production, Quality, and Safety in Developing Countries' hosted by the Feed the Future Innovation Lab for Livestock Systems (FFILLS) of the University of Florida, at the American Dairy Science Association's annual meeting in Cincinnati, Ohio on June 23-26, 2019. I am most grateful to Dr Adegbola Adesogan, Director of FFILLS for his invitation and support to attend the event.

REFERENCES

Abdalla, H. M., J. E. Ntwenya, E. Paul, M. Huang, and S. Vuai. 2017. Socio-economic and spatial correlates of subclinical iodine deficiency among pregnant women age 15–49 years in Tanzania. BMC Nutrition 3:47.

Abdullah, A., A. Peeters, M. de Courten, and J. Stoelwinder. 2010. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res. Clin. Pract. 89:309-319. https://doi.org/10.1016/j.diabres.2010.04.012

Abrams, S. A., Z. Chen, and K. M. Hawthorne. 2014. Magnesium metabolism in 4-year-old to 8-year-old children. J. Bone Miner. Res. 29:118–122. https://doi.org/10.1002/jbmr.2021

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Astrup, A., H. C. S. Bertram, J.-P. Bonjour, L .C. P. de Groot, M. C. de Oliveira Otto, E. L. Feeney, M. L. Garg, D. I. Givens, F. J. Kok, R. M. Krauss, B. Lamarche, J.-M. Lecerf, P. Legrand, M. McKinley, R. Micha, M.-C. Michalski, D. Mozaffarian, and S. S. Soedamah-Muthu. 2019. WHO draft guidelines on dietary saturated and trans fatty acids: time for a new approach? BMJ. 365:l4137. https://doi.org/10.1136/bmj.l4137

Baker, I. A., P. C. Elwood, J. Hughes, M. Jones, F. Moore, and P. Sweetnam. 1980. A randomised controlled trial of the effect of the provision of free school milk on the growth of children. J. Epidemiol. Community Health. 34:31-34. https://doi.org/10.1136/jech.34.1.31

Bates, B., A. Lennox, A. Prentice, C. Bates, P. Page, S. Nicholson, and G. Swan. 2014. *National Diet and Nutrition Survey, Results from Years 1-4 (combined) of the Rolling Programme (2008/2009-2011/12).* A survey carried out on behalf of Public Health England and the Food Standards Agency, London, UK.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/594361/NDNS_Y1_to_4_UK_report_full_text_revised_February_2017.pdf

Bath, S. C., S. Button, and M. P. Rayman, 2012. Iodine concentration of organic and conventional milk: implications for iodine intake. Br. J. Nutr. 107:935-940. https://doi.org/10.1017/S0007114511003059

Bath, S. C., M. P. Rayman, C. D.Steer, J. Golding, and P. Emmett, 2013. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). The Lancet. 382:331-337.

Bath, S. C., A. Walter, A. Taylor, J. Wright, and M. P. Rayman, 2014. Iodine deficiency in pregnant women living in the South East of the UK: the influence of diet and nutritional supplements on iodine status. Br. J. Nutr. 111:1622-1631.

epted version before proof

884 Bath, S. C., and M. P. Rayman, 2015. A review of the iodine status of UK pregnant women
885 and its implications for the offspring. Environ. Geochem. Health. 27:619-629.

886 Bath, S. C., S. Hill, H. G. Infante, S. Elghul, C. J. Nezianya, and M. P. Rayman. 2017. Iodine
887 concentration of milk-alternative drinks available in the UK in comparison to cows' milk. Br.
888 J. Nutr. 118: 525–532.

889 Batty, B. S., and M. Bionaz, 2019. The milk behind the moustache: A review of milk and bone
890 biology. J. Dairy Sci. 102:7608-7617.

891 Benjamin, E. J. et al. (+50 authors), 2018. Heart Disease and Stroke Statistics-2018 Update.
892 Circulation. 137:e67–e492

893 Bischoff-Ferrari, H. A., B. Dawson-Hughes, J. A. Baron, J. A. Kanis, E. J. Orav, H. B.
894 Staehelin, P. Kiel, P. Burckhardt, J. Henschkowski, D. Spiegelman, R. Li, J. B. Wong, D.
895 Feskanich, and W. C. Willett. 2011. Milk intake and risk of hip fracture in men and women; a
896 meta-analysis of prospective cohort studies. J. Bone Miner. Res. 26: 833-839.

897 Black, R. E., S. M. Williams, I. E. Jones, and A. Goulding. 2002. Children who avoid drinking
898 cow milk have low dietary calcium intakes and poor bone health. Am. J. Clin. Nutr. 76:675–
899 680.

900 Bougma, K., F. E. Aboud, K. B. Harding, and G. S. Marquis. 2013. Iodine and mental
901 development of children 5 years old and under: A systematic review and meta-analysis.
902 Nutrients. 5:1384-1416.

903 Brantsæter, A. L., M. H. Abe, M. Haugen, and H. M. Meltzer. 2013. Risk of suboptimal iodine
904 intake in pregnant Norwegian women. Nutrients 5:424-440.

905 Businge, C. B., N. Madini, B. Longo-Mbenza, and A. P. Kengne. 2019. Insufficient iodine
906 nutrition status and the risk of pre-eclampsia: a protocol for systematic review and meta-
907 analysis. BMJ Open. 9:e025573.

Accepted version before proof

908 Campbell, W. W., T. A. Trappe, R. R. Wolfe, and W. J. Evans. 2001. The recommended dietary
909 allowance for protein may not be adequate for older people to maintain skeletal muscle. J.
910 Gerontol. A Biol. Sci. Med. Sci. 56:M373–M380.

911 Cashman, K. D., K. G. Dowling, Z. Skrabáková, M. Gonzalez-Gross, J. Valtueña, S. De
912 Henauw, L. Moreno, C. T. Damsgaard, K. F. Michaelsen, C. Mølgaard, R. Jorde, G. Grimnes,
913 G. Moschonis, C. Mavrogianni, Y. Manios, M. Thamm, G. B. M. Mensink, M. Rabenberg, M.
914 A. Busch, L. Cox, S. Meadows, G. Goldberg, A. Prentice, J. M. Dekker, G. Nijpels, S. Pilz, K.
915 M. Swart, N. M. van Schoor, P. Lips, G. Eiriksdottir, V. Gudnason, M. F. Cotch, S. Koskinen,
916 C. Lamberg-Allardt, R. A. Durazo-Arvizu, C. T. Sempos, and M. Kiely. 2016. Vitamin D
917 deficiency in Europe: pandemic? Am. J. Clin. Nutr. 103:1033–1044.

918 Chen, M., A. Pan, V. S. Malik, and F. B. Hu. 2012. Effects of dairy intake on body weight and
919 fat: A meta-analysis of randomized controlled trials. Am. J. Clin. Nutr. 96:735–747.

920 Cockcroft, J. R., and I. B. Wilkinson. 2000. Large arterial stiffness: an important therapeutic
921 target. J. Hum. Hypertens.14:533-535.

922 Corry Mann, H. C. 1926. Diets for boys during the school age. Medical Research Council
923 Special Report Series No. 105. HMSO: London.

924 Crichton, G. E., M. F. Elias, G. A. Dore, A. P Abhayaratna, and M. A. Robbins. 2012. Relations
925 between dairy food intake and arterial stiffness. Hypertension. 59:1044-1051.

926 Costeira, M. J., P. Oliveira, N. C. Santos, S. Ares, B. Saenz-Rico, G. M. de Escobar, and J. A.
927 Palha. 2011. Psychomotor development of children from iodine-deficient region. J. Pediatr.
928 159:447-453.

929 Cruz-Jentoft, A. J., G. Bahat, J. Bauer, Y. Boirie, O. Bruyère, T. Cederholm, C. Cooper, F.
930 Landi, Y. Rolland, A. A. Sayer, S. M. Schneider, C. C. Sieber, E. Topinkova, M.
931 Vandewoude, M. Visser, M. Zamboni, Writing Group for the European Working Group on

Accepted version before proof

Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. 2019. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 48:16-31.

Choudhury, S., and D. D. Headey. 2018. Household dairy production and child growth: Evidence from Bangladesh. Econ. Hum. Biol. 30:150–161. https://doi.org/10.1016/j.ehb.2018.07.001

de Goede, J., S. S. Soedamah-Muthu, A. Pan, L. Gijsbers, and J. M. Geleijnse. 2016. Dairy Consumption and Risk of Stroke: A Systematic Review and Updated Dose–Response Meta-Analysis of Prospective Cohort Studies. J. Am. Heart Assoc. 5:e002787.

Dehghan, M., A. Mente, S. Rangarajan, P. Sheridan, V. Mohan, R. Iqbal, R. Gupta, S. Lear, E. Wentzel-Viljoen, A. Avezum, P. Lopez-Jaramillo, P. Mony, R. P. Varma, R. Kumar, J. Chifamba, K. F. Alhabib, N. Mohammadifard, A. Oguz, F. Lanas, D. Rozanska, K. B. Bostrom, K. Yusoff, L. P. Tsolkile, A. Dans, A. Yusufali, A. Orlandini, P. Poirier, R. Khatib, B. Hu, L. Wei, L. Yin, A. Deeraili, K. Yeates, R. Yusuf, N. Ismail, D. Mozaffarian, K. Teo, S. S. Anan, and S. Yusuf on behalf of the Prospective Urban Rural Epidemiology (PURE) study investigators. 2018. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. The Lancet. 392:10161, 2288-2297. http://dx.doi.org/10.1016/S0140-6736(18)31812-9

de Onis, M., and F. Branca. 2016. Childhood stunting: a global perspective. Matern. Child Nutr. 12 (Suppl. 1):12–26.

Department of Health. 1991. Dietary Reference Values, A Guide. London: HMSO 51pp.

Devries, M. C., A. Sithamparapillai, K. S. Brimble, L. Banfield, R. W. Morton, and S. M. Phillips. 2018a. Changes in kidney function do not differ between healthy adults consuming higher compared with lower- or normal-protein diets: A systematic review and meta-analysis. J. Nutr. 148:1760–1775.

Accepted version before proof

956 Devries, M. C., C. McGlory, D. R. Bolster, A. Kamil, M. Rahn, L. Harkness, S. K. Baker, and
957 S. M. Phillips. 2018b. Leucine, not total protein, content of a supplement is the primary
958 determinant of muscle protein anabolic responses in healthy older women. J. Nutr.148:1088–
959 1095.

960 Diabetes UK. 2019. Number of people with diabetes reaches 4.7 million. Available at:
961 https://www.diabetes.org.uk/about_us/news/new-stats-people-living-with-diabetes

962 Dougkas, A., C. K. Reynolds, D. I. Givens, P. C. Elwood, and A. M. Minihane. 2011.
963 Associations between dairy consumption and body weight: A review of the evidence and
964 underlying mechanisms. Nutr. Res. Rev. 24:72–95.

965 Dougkas, A., S. Barr, S. Reddy, and C. D. Summerbell. 2019. A critical review of the role of
966 milk and other dairy products in the development of obesity in children and adolescents. Nutr.
967 Res. Rev. 32:106-127.

968 Du, X., K. Zhu, A. Trube, Q. Zhang, G. Ma, X. Hu, D.R. Fraser, and H. Greenfield. 2004.
969 School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls
970 aged 10–12 years in Beijing. Br. J. Nutr. 92:159-168.

971 Erem, S., A. Atfi, and M. S. Razzaque. 2019. Anabolic effects of vitamin D and magnesium in
972 aging bone. J. Steroid Biochem. Mol. Biol. 193: 105400.

973 European Commission. 2005. Council Regulation (EC) No 1459/2005 of 08 September 2005
974 amending the condition of authorization of a number of feed additives belonging to the group
975 of trace elements. Official Journal of the European Union. L 233:8-10.

976 Fabiani, R., G. Naldini, and M. Chiavarini. 2019. Dietary patterns in relation to low bone
977 mineral density and fracture risk: A systematic review and meta-analysis. Adv. Nutr. 10: 219-
978 236.

Accepted version
Before proof

979 FAO/WHO/UNU. 2007. Protein and amino acid requirements in human nutrition. Report of a
980 joint FAO/WHO/UNU expert consultation (WHO Technical Report Series 935), 265pp.

981 Feeney, E. L., R. Barron, V. Dible, Z. Hamilton, Y. Power, L. Tanner, C. Flynn, P. Bouchier,
982 T. Beresford, N. Noronha, and E. R. Gibney. 2018. Dairy matrix effects: response to
983 consumption of dairy fat differs when eaten within the cheese matrix-a randomized controlled
984 trial. Am J Clin. Nutr. 108:1-8.

985 Fekete, Á. A., D. I. Givens, and J. A. Lovegrove. 2013. The impact of milk proteins and
986 peptides on blood pressure and vascular function: a review of evidence from human
987 intervention studies. Nutr. Res. Rev. 26:177-190.

988 Fekete, Á. A., C. Giromini, Y. Chatzidiakou, D. I. Givens, and J. A. Lovegrove. 2016. Whey
989 protein lowers blood pressure and improves endothelial function and lipid biomarkers in adults
990 with prehypertension and mild hypertension: results from the chronic Whey2Go randomized
991 controlled trial. Am. J. Clin. Nutr. 104:1534-154.

992 Fekete, Á. A., C. Giromini, Y. Chatzidiakou, D. I. Givens, and J. A. Lovegrove. 2018. Whey
993 protein lowers systolic blood pressure and Ca-caseinate reduces serum TAG after a high-fat
994 meal in mildly hypertensive adults. Sci. Rep. 8:5026.

995 Feskanich, D., H. A. Bischoff-Ferrari, L. Frazier, and W. C. Willett. 2014. Milk consumption
996 during teenage years and risk of hip fractures in older adults. JAMA Pediatr. 168:54-60.

997 Feskanich, D, H. E. Meyer, T. T. Fung, H. A. Bischoff-Ferrari, and W. C. Willett. 2018. Milk
998 and other dairy foods and risk of hip fracture in men and women. Osteoporos. Int. 29: 385-396.
999 https://doi.org/10.1007/s00198-017-4285-8

1000 Figueroa, A., A. Wong, A. Kinsey, R. Kalfon, W. Eddy, and M. J. Ormsbee. 2014. Effects of
1001 milk proteins and combined exercise training on aortic hemodynamics and arterial stiffness in
1002 young obese women with high blood pressure Am. J. Hypertens. 27:338-344.

Accepted for proof

1003 FitzGerald, R. J., and H. Meisel. 2000. Milk protein-derived peptide inhibitors of angiotensin-
1004 1-converting enzyme. Br. J. Nutr. 84: Suppl. 1, S33-S37.

1005 Flachowsky, G., K. Franke, U. Meyer, M. Leiterer, and F. Schöne. 2014. Influencing factors
1006 on iodine content of cow milk. Eur. J. Nutr. 53: 351-365.
1007 https://link.springer.com/article/10.1007/s00394-013-0597-4

1008 Food Standards Agency. 2008. *Retail Survey of Iodine in UK Produced Dairy Foods, FSIS*
1009 *02/08.* London: Food Standards Agency.

1010 Forbes, E. E., and R. E. Dahl. 2010. Pubertal development and behavior: Hormonal activation
1011 of social and motivational tendencies. Brain Cogn. 72:66-72.

1012 Fourreau, D., N. Peretti, B. Hengy, Y. Gillet, S. Courtil-Teyssedre, L. Hess, I. Loras-Duclaux,
1013 N. Caron, C. Didier. F. Cour-Andlauer, S. Heissat, A. Lachaux, and É. Javouhey. 2013.
1014 Complications carentielles suite à l'utilisation de laits végéaux, chez des nourrissons de deux
1015 mois et demi à 14 mois (quatre cas). Presse Med. 42:e37-43. doi: 10.1016/j.lpm.2012.05.029

1016 Gatineau, M., C. Hancock, N. Holman, H. Outhwaite, L. Oldridge, C. Anna, and L. Ells.
1017 2014. Adult Obesity and Type 2 diabetes. PHE publications gateway number: 2014211.
1018 Public Health England, London.
1019 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data
1020 /file/338934/Adult_obesity_and_type_2_diabetes_.pdf

1021 Gijsbers, L., E. L. Ding, V. S. Malik, J. de Goede, J. M. Geleijnse, and S. S. Soedamah-Muthu.
1022 2016. Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of
1023 observational studies. Am. J. Clin. Nutr. 103:1111-1124.

1024 Giromini, C., Á. A. Fekete, D. I. Givens, A. Baldi, and J. A. Lovegrove. 2017. A comparison
1025 of the in vitro angiotensin-converting enzyme inhibitory capacity of dairy and plant protein
1026 supplements. Nutrients 9:1352.

Accepted version before proof

1027 Giromini, C., J. A. Lovegrove, D. I. Givens, R. Rebucci, L. Pinotti, E. Maffioli, G. Tedeschi,
1028 and A. Baldi. 2019. In vitro digested milk proteins: evaluation of angiotensin-converting
1029 enzyme inhibitory and antioxidant activities, peptidomic profile and mucin gene expression in
1030 HT29-MTX cells. J. Dairy Sci. in press.

1031 Goldacre, M., N. Hall, and D. G. R.Yeates. 2014. Hospitalisation for children with rickets in
1032 England: a historical perspective. The Lancet 383:597-598.

1033 Grant, C. A., and A. L. Hicks. 2018. Comparative life cycle assessment of milk and plant-
1034 based alternatives. Environ. Eng. Sci. 35: 1235-1247.

1035 Griffin, B. A. and J. A. Lovegrove. 2018. Butter increases HDL functional capacity: Is this
1036 compensation for its adverse effect on serum LDL cholesterol? J. Nutr. 148: 1069-1070.

1037 Gullberg, B., O. Johnell, and J. A. Kanis. 1997. World-wide projections for hip fracture.
1038 Osteoporosis Int. 7:407-413. https://link.springer.com/article/10.1007/PL00004148

1039 Guo, J., A. Dougkas, P. C. Elwood, and D. I. Givens. 2018. Dairy foods and body mass index
1040 over 10-Year: Evidence from the Caerphilly prospective cohort study. Nutrients 10:1515.

1041 Guo, J., A. Astrup, J. A. Lovegrove, L. Gijsbers, D. I. Givens, and S. S. Soedamah-Muthu.
1042 2017. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality:
1043 dose-response meta-analysis of prospective cohort studies. Eur. J. Epidemiol. 32:269–287.

1044 Guo, J., D. I. Givens, A. Astrup, S. J. L. Bakker, G. H. Goossens, M. Kratz, A. Marette, H. Pijl,
1045 and S. S. Soedamah-Muthu. 2019. The impact of dairy products in the development of type 2
1046 diabetes: where does the evidence stand in 2019? Advances in Nutrition. Published on line
1047 ahead of print, available at: https://doi.org/10.1093/advances/nmz050

1048 Hernlund, E., A. Svedbom, M. Ivergård, J. Compston, C. Cooper, J. Stenmark, E. V.
1049 McCloskey, B. Jönsson, and J. A. Kanis. 2013. Osteoporosis in the European Union: medical
1050 management, epidemiology and economic burden. Arch. Osteoporos. 8:136.

ion before proof

1051 Hjerpsted, J., E. Leedo, and T. Tholstrup. 2011. Cheese intake in large amounts lowers LDL-
1052 cholesterol concentrations compared with butter intake of equal fat content. Am. J. Clin. Nutr.
1053 94:1479–1484.

1054 Holick, M. F. 2010. The vitamin D deficiency pandemic: a forgotten hormone important for
1055 life. Public Health Rev. 32:267-283

1056 Host, A., and S. Halken. 2014. Cow's milk allergy: where have we come from and where are
1057 we going? Endocr. Metab. Immune Disord. Drug Targets. 14:2-8.

1058 Hoppe, C., C. Mølgaard, C. Dalum, A. Vaag, and K. F. Michaelsen. 2009. Differential effects
1059 of casein versus whey on fasting plasma levels of insulin, IGF-1 and IGF-1/IGFBP-3: results
1060 from a randomized 7-day supplementation study in pre-pubertal boys. Eur. J. Clin. Nutr. 63:
1061 1076–1083.

1062 Hu, F. B., J. E. Manson, M. J. Stampfer, G. Colditz, S. Liu, C. G. Solomon, and W. C. Willett.
1063 2001. Diet, lifestyle and the rise of type 2 diabetes in women. N. Engl. J. Med. 345:790–797.

1064 Hunter, G. R., H. Singh, S. J. Carter, D. R. Bryan, and G. Fisher. 2019. Sarcopenia and its
1065 implications for metabolic health. J. Obes. 2019: Article ID 8031705.
1066 https://doi.org/10.1155/2019/8031705

1067 Hynes, K. L., P. Otahal, I. Hay, and J. R. Burgess. 2013. Mild iodine deficiency during
1068 pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up
1069 of the gestational iodine cohort. J. Clin. Endocrinol. Metab. 98: 1954-1962.

1070 Itkonen, S. T., M. Erkkola, and C. J. E. Lamberg-Allardt. 2018. Vitamin D fortification of fluid
1071 milk products and their contribution to vitamin D intake and vitamin D status in observational
1072 studies – a review. Nutrients 10:1054. doi: 10.3390/nu10081054.

ted version proof

1073 Iguacel, I., M. L. Miquel-Berges, A. Gómez-Bruton, L. A. Moreno, and C. Julián. 2018.
1074 Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and
1075 meta-analysis. Nutr. Rev. 77: 1-18.

1076 Jazayeri, M., Y. Moradi, A. Rasti, M. Nakhjavani, M. Kamali, and H. R. Baradaran. 2018.
1077 Prevalence of vitamin D deficiency in healthy Iranian children: a systematic review and meta-
1078 analysis. Med. J. Islam Repub. 32:83. Iran doi: 10.14196/mjiri.32.83. eCollection 2018.

1079 Kanis. J. A., H. Johansson, A. Oden, C. De Laet, O. Johnell, J. A. Eisman, E. McCloskey, D.
1080 Mellstrom, H. Pols, J. Reeve, A. Silman, and A. A. Tenenhouse. 2005. Meta-analysis of milk
1081 intake and fracture risk: low utility for case finding. Osteoporos. Int. 16: 799-804.

1082 Kalkwarf, H. J., J. C. Khoury, and B. P. Lanphear. 2003. Milk intake during childhood and
1083 adolescence, adult bone density, and osteoporotic fractures in US women. Am. J. Clin. Nutr.
1084 77: 257-265.

1085 Kang, K., O. F. Sotunde, and H. A. Weiler. 2019. Effects of milk and milk product consumption
1086 on growth among children and adolescents aged 6-18 years: A meta-analysis of randomized
1087 controlled trials. Adv. Nutr. 10:250-261.

1088 Kouw, I. W. K., A. M. Holwerda, J. Trommelen, I. F. Kramer, J. Bastiaanse, S. L. Halson, W.
1089 K. W. H. Wodzig, L. B. Verdijk, and L. J. C. van Loon. 2017. Protein ingestion before sleep
1090 increases overnight muscle protein synthesis rates in healthy older men: A randomized
1091 controlled trial. J. Nutr. 147:2252-2261.

1092 Kratz, M., T. Baars, and S. Guyenet. 2013. The relationship between high-fat dairy
1093 consumption and obesity, cardiovascular, and metabolic disease. Eur. J. Nutr. 52:1-24.

1094 Kris-Etherton, P. M., J. A. Grieger, H. F. Hilpert, and S. G. West. 2009. Milk products, dietary
1095 patterns and blood pressure management. J. Am. Coll. Nutr. 28: Suppl 1:103S-119S.

Accepted version before proof

1096 Kunutsor, S. K., M. R. Whitehouse, A. W. Blom, and J. A. Laukkanen. 2017. Low serum
1097 magnesium levels are associated with increased risk of fractures: a long-term prospective
1098 cohort study. Eur. J. Epidemiol. 32:593-603.

1099 Larson, N. I., D. Neumark-Sztainer, L. Harnack, M. Wall, M. Story, and M. E. Eisenberg. 2009.
1100 Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and
1101 correlates of calcium intake. J. Nutr. Educ. Behav. 41:254-260.

1102 Le Louer, B., J. Lemale, K. Garcette, C. Orzechowski, A. Chalvon, J.-P.Girardet, and P.
1103 Tounian. 2014. Conséquences nutritionnelles de l'utilisation de boissons végétales inadaptées
1104 chez les nourrissons de moins d'un an. Arch Pediatrie 21:483-488.

1105 Lee, K. W., D. Shin, M. S. Cho, and W. O. Song. 2016. Food group intakes as determinants of
1106 iodine status among us adult population. Nutrients 8:325.

1107 Leroy, J. L., and E. A. Frongillo. 2019. Perspective: What does stunting really mean? A critical
1108 review of the evidence. Adv. Nutr. 10:196-204.

1109 Livingstone, K. M., J. A. Lovegrove, J. R. Cockcroft, P. C. Elwood, J. E. Pickering, and D. I.
1110 Givens. 2013. Does dairy food intake predict arterial stiffness and blood pressure in men?
1111 Evidence from the Caerphilly Prospective Study. Hypertension 61:42-47.

1112 Locatelli, V., and V. E. Bianchi. 2014. Effect of GH/IGF-1 on bone metabolism and
1113 osteoporosis. Int. J. Endocrinol. 2014: Article ID 235060.

1114 Lonnie, M., E. Hooker, J. M. Brunstrom, B. M. Corfe, M. A. Green, A. W. Watson, E. A.
1115 Williams, E. J. Stevenson, S. Penson, and A. M. Johnstone. 2018. Protein for Life: Review of
1116 optimal protein intake, sustainable dietary sources and the effect on appetite in ageing adults.
1117 Nutrients 10:360.

Accepted version before proof

1118 Lu, L., P. Xun, Y. Wan, K. He, and W. Cai. 2016. Long-term association between dairy
1119 consumption and risk of childhood obesity: a systematic review and meta-analysis of
1120 prospective cohort studies. Eur. J. Clin. Nutr. 70:414-423.

1121 Ma, X., Z. Huang, X. Yang, and Y. Su. 2014. Calcium supplementation and bone mineral
1122 accretion in Chinese adolescents aged 12–14 years: a 12-month, dose-response, randomised
1123 intervention trial. Br. J. Nutr. 112:1510-1520.

1124 Michaelsen, K. F. 2013. Cow's milk in the prevention and treatment of stunting and wasting.
1125 Food Nutr. Bull. 34:249-251.

1126 Michaëlsson, K., A. Wolk, S. Langenskiöld, S. Basu, E. W. Lemming, H. Melhus, and L.
1127 Byberg. 2014. Milk intake and risk of mortality and fractures in women and men: cohort
1128 studies. BMJ 349:g6205.

1129 Miles, E. A. 2020. Adverse reactions to cow's milk. Pages 271-297 in Milk and Dairy Foods:
1130 Their Functionality in Human Health and Disease. D. I. Givens, ed. Elsevier, Cambridge, MA
1131 02139, United States.

1132 Mullen, K., L. Hamill, K. Doolan, I. Young, P. Smyth, A. Flynn, J. Walton, A. A. Meharg, M.
1133 Carey, C. McKernan, M. Bell, N. Black, U. Graham, D. McCance, C. McHugh, P. McMullan,
1134 S. McQuaid, A. O'Loughlin, A. Tuthill, S. C. Bath, M. Rayman, and J. V. Woodside. 2019.
1135 Iodine status of teenage girls on the island of Ireland. Eur. J. Nutr. Epub ahead of print at:
1136 https://doi.org/10.1007/s00394-019-02037-x.

1137 Munblit, D., M. R. Perkin, D. J. Palmer, K. J. Allen, and R. J. Boyle. 2020. Assessment of
1138 evidence about common infant symptoms and cow's milk allergy. JAMA Pediatr. Published
1139 online April 13, 2020. doi:10.1001/jamapediatrics.2020.0153

Accepted version before proof

National Statistics. 2017a. Health Survey for England 2016, Summary of Key Findings. Government Statistical Service, available at: https://files.digital.nhs.uk/pdf/s/q/hse2016-summary.pdf

National Statistics. 2017b. Health Survey for England 2016, Adult Health Trends. Government Statistical Service, available at: http://healthsurvey.hscic.gov.uk/media/63757/HSE2016-Adult-trends.pdf

NHS. 2019. Stages of puberty. Available at: https://www.nhs.uk/live-well/sexual-health/stages-of-puberty-what-happens-to-boys-and-girls/

Nittari, G., S. Scuri, F. Petrelli, I. Pirillo, N. M. di Luca, and I. Grappasonni. 2019. Fighting obesity in children from European World Health Organization member states. Epidemiological data, medical-social aspects, and prevention programs. Clin. Ter. 170:e223-230.

http://www.clinicaterapeutica.it/ojs/index.php/ClinicaTerapeutica/article/view/427/169

O'Brien, B., D. Gleeson, and K. Jordan. 2013. Iodine concentrations in milk. Irish J. Agr. Food Res. 52:209-216.

OECD. 2017. Obesity Update. Available at: www.oecd.org/health/obesity-update.htm

O'Kane, S. M., L. K. Pourshahidi, M. S. Mulhern, J. J. Strain, E. M. Mackle, D. Koca, L. Schomburg, S. Hill, J. O'Reilly, D. Kmiotek, C. Deitrich, S. C. Bath, and A. J. Yeates. 2018. Cow milk consumption increases iodine status in women of childbearing age in a randomized controlled trial. J. Nutr. 148:401-408. https://doi.org/10.1093/jn/nxx043

Ong, A. M., K. Kang, H. A. Weiler, and S. N. Morin. 2019. Fermented milk products and bone health in postmenopausal women: A systematic review of randomized controlled trials, prospective cohorts, and case-control studies. Adv. Nutr. 00: 1-15.

https://doi.org/10.1093/advances/nmz108

Accepted version

1163 Paddon-Jones, D, and B. B. Rasmussen. 2009. Dietary protein recommendations and the
1164 prevention of sarcopenia: Protein, amino acid metabolism and therapy. Curr. Opin. Clin. Nutr.
1165 Metab. Care 12:86-90.

1166 Pastuszka, R., J. Barłowska, and Z. Litwińczuk. 2016. Allergenicity of milk of different animal
1167 species in relation to human milk. Postepy Hig. Med. Dosw. 70:1451-1459.

1168 Payling, L. M., D. T. Juniper, C. Drake, C. Rymer, and D. I. Givens. 2015. Effect of milk
1169 type and processing on iodine concentration of organic and conventional winter milk at retail:
1170 implications for nutrition. Food Chem. 178:327-330.

1171 Pimpin, L., J. H. Y. Wu, H. Haskelberg, L. Del Gobbo, and D. Mozaffarian. 2016. Is butter
1172 back? A systematic review and meta-analysis of butter consumption and risk of
1173 cardiovascular disease, diabetes, and total mortality. PLoS ONE 11:e0158118.

1174 Prentice, A. 2013. Nutritional rickets around the world. J. Steroid Biochem. 136:201-206.

1175 Quann, E. E., V. L. Fulgoni 111, and N. Auestad. 2015. Consuming the daily recommended
1176 amounts of dairy products would reduce the prevalence of inadequate micronutrient intakes in
1177 the United States: diet modeling study based on NHANES 2007-2010. Nutr. J. 14: 90.

1178 Rangel, A. H. do N., D. C. Sales, S. A. Urbano, J. G. B. Galvão Júnior, J. C. de Andrade Neto,
1179 and C. de S. Macêdo. 2016. Lactose intolerance and cow's milk protein allergy. Food Sci.
1180 Technol. (Campinas).36 April/June Epub: https://doi.org/10.1590/1678-457X.0019

1181 Roberts, C., T. Steer, N. Maplethorpe, L. Cox, S. Meadows, S. Nicholson, P. Page, and G.
1182 Swan. 2018. National Diet and Nutrition Survey. Results from Years 7-8 (combined) of the
1183 Rolling Programme (2014/15 to 2015/16). PHE Publication gateway number: 2017851 Public
1184 Health England, London.

1185 Roser, M. 2017. Life Expectancy. Retrieved on 5 June 2017 from
1186 https://ourworldindata.org/life-expectancy/

Accepted version before proof

1187 Rosqvist, F., A. Smedman, H. Lindmark-Mansson, M. Paulsson, P. Petrus, S. Straniero, M.
1188 Rudling, I. Dahlman, and U. Risérus. 2015. Potential role of milk fat globule membrane in
1189 modulating plasma lipoproteins, gene expression, and cholesterol metabolism in humans: a
1190 randomized study. Am. J. Clin. Nutr. 102: 20-30.

1191 Sahni S., K. M. Mangano, D. P. Kiel, K. I. Tucker, and M. T. Hannan. 2017. Dairy intake is
1192 protective against bone loss in older vitamin D supplement users: The Framingham Study. J.
1193 Nutr. 147, 645-652.

1194 Scrafford, C. G., X. Bi, J. K. Multani, M. M. Murphy, J. K. Schmier, and L. M. Barraj. 2020.
1195 Health care costs and savings associated with increased dairy consumption among adults in the
1196 United States. Nutrients 12: 233. doi:10.3390/nu12010233

1197 Schoz-Ahrens, K. E., F. Ahrens, and C. A. Barth. 2019. Nutritional and health attributes of
1198 milk and milk imitations. Eur. J. Clin. Nutr. Epub ahead of print:
1199 https://doi.org/10.1007/s00394-019-01936-3.

1200 Semali, I. A., A. Tengia-Kessy, E. J. Mmbaga, and G. Leyna. 2015. Prevalence and
1201 determinants of stunting in under-five children in central Tanzania: remaining threats to
1202 achieving Millennium Development Goal 4. BMC Public Health 15:1153.
1203 https://dx.doi.org/10.1186%2Fs12889-015-2507-6

1204 Shafiee, G., A. Keshtkar, A. Soltani, Z. Ahadi, B. Larijani, and R. Heshmat. 2017. Prevalence
1205 of sarcopenia in the world: a systematic review and meta- analysis of general population
1206 studies. J. Diabetes Nutr. Metab. Dis. 16:21.

1207 Średnicka-Tober, D., M. Barański, C. J. Seal, R. Sanderson, C. Benbrook, H. Steinshamn, J.
1208 Gromadzka-Ostrowska, E. Rembiałkowska, K. Skwarło-Sońta, M. Eyre, G. Cozzi, M. K.
1209 Larsen, T. Jordon, U. Niggli, T. Sakowski, P. C. Calder, G. C. Burdge, S. Sotiraki, A.
1210 Stefanakis, S. Stergiadis, H. Yolcu, E. Chatzidimitriou, G. Butler, G. Stewart, and C. Leifert.

Accepted version before p

1211 2016. Higher PUFA and n-3 PUFA, conjugated linoleic acid, α-tocopherol and iron, but lower
1212 iodine and selenium concentrations in organic milk: a systematic literature review and meta-
1213 and redundancy analyses. Br. J. Nutr. 115:1043-1060.

1214 Soedamah-Muthu, S. S., and J. de Goede. 2018. Dairy consumption and cardiometabolic
1215 diseases: systematic review and updated meta-analyses of prospective cohort studies. Curr.
1216 Nutr. Rep. 7:171-172.

1217 Steinberger, J., S. R. Daniels, N. Hagberg, C. R. Isasi, A. S. Kelly, D. Lloyd-Jones, R. R. Pate,
1218 C. Pratt, C. M. Shay, J. A. Towbin, E. Urbina, L. V. Van Horn, and J. P. Zachariah. 2016.
1219 Cardiovascular health promotion in children: challenges and opportunities for 2020 and
1220 beyond. Circulation 134:e236–e255.

1221 Stevenson, M. C., C. Drake, and D. I. Givens. 2018. Further studies on the iodine concentration
1222 of conventional, organic and UHT semi-skimmed milk at retail in the UK. Food Chem. 239:
1223 551-555.

1224 Thacher, T. D., P. R. Fischer, P. J. Tebben, R. J. Singh, S. S. Cha, J. A. Maxson, and B. P.
1225 Yawn. 2013. Increasing incidence of nutritional rickets: A population-based study in Olmsted
1226 County, Minnesota. Mayo Clin. Proc. 88:176-183.

1227 Thorning, T. K., H. C. Bertram, J.-P. Bonjour, L. de Groot, D. Dupont, E. Feeney, R. Ipsen, J.-
1228 M. Lecerf, A. Mackie, M. C. McKinley, M.-C. Michalski, D. Rémond, U. Risérus, S.
1229 Soedamah-Muthu, T. Tholstrup, C. Weaver, A. Astrup, and D. I. Givens. 2017. Whole dairy
1230 matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps.
1231 Am. J. Clin. Nutr. 105:1033-1045.

1232 Totzauer, M., V. Luque, J. Escribano, R. Closa-Monasterolo, E. Verduci, A. ReDionigi, J.
1233 Hoyos, J.-P. Langhendries, D. Gruszfeld, P. Socha, B. Koletzko, and V. Grote. 2018. Effect of
1234 lower versus higher protein content in infant formula through the first year on body

Accepted version before proof

composition from 1 to 6 years: follow-up of a randomized clinical trial. Obesity 26: 1203–1210.

Turner, P. J., M. H. Gowland, V. Sharma, D. Ierodiakonou, N. Harper, T. Garcez, R. Pumphrey, and R. J. Boyle. 2015. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012. J. Allergy Clin. Immunol. 135:956-963.

van Mil, N. H., H. Tiemeier, J. J. Bongers-Schokking, A. Ghassabian, A. Hofman, H. Hooijkaas, V. W. V. Jaddoe, S. M. de Muinck Keizer-Schrama, E. A. P. Steegers, T. J. Visser, W. Visser, H. A. Ross, F. C. Verhulst, Y. B. de Rijke, R. P. M. Steegers-Theunissen. 2012. Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. J. Nutr. 142:2167-2174. https://doi.org/10.3945/jn.112.161950

Vanderpump, M. P. J., J. H. Lazarus, P. P. Smyth, P. Laurberg, R. L. Holder, K. Boelaert, and J. A. Franklyn. 2011. Iodine status of UK schoolgirls: a cross-sectional survey. The Lancet 377, 2007-2012.

Vojdani, A., C. Turnpaugh, and E. Vojdani. 2018. Immune reactivity against a variety of mammalian milks and plant-based milk substitutes. J. Dairy Res. 85:358–365.

Wan, X., S. Wang, J. Xu, L. Zhuang, K. Xing, M. Zhang, X. Zhu, L. Wang, P. Gao, Q. Xi1, J. Sun, Y. Zhang, T. Li, G. Shu, and Q. Jiang. 2017. Dietary protein-induced hepatic IGF-1 secretion mediated by PPARγ activation. PLoS ONE 12:e0173174.

Wall, B., H. Hamer, A. de Lange, A. Kiskini, B. B. Groen, J. M. Senden, A. P. Gijsen, L. B. Verdijk, and L. J. van Loon. 2013. Leucine co-ingestion improves post-prandial muscle protein accretion in elderly men. Clin. Nutr. 32:412-419.

Wall, B. T., N. M. Cermak, and L. J. C. van Loon. 2014. Dietary protein considerations to support active aging. Sports Med. 44 (Suppl 2):S185-S194.

Accepted version before proof

1259 Weaver, C. M., C. M. Gordon, K. F. Janz, H. J. Kalkwarf, J. M. Lappe, R. Lewis, M. O'Karma,
1260 T. C. Wallace, and B. S. Zemel. 2016. The National Osteoporosis Foundation's position
1261 statement on peak bone mass development and lifestyle factors: a systematic review and
1262 implementation recommendations. Osteoporosis Int. 27:1281-1386.

1263 Welch, A. A., J. Skinner and M. Hickson. 2017. Dietary magnesium may be protective for
1264 aging of bone and skeletal muscle in middle and younger older mem and women. Nutrients 9:
1265 1189.

1266 WHO. 1999. Technical Report Series 886. Programming for adolescent health and
1267 development, Geneva, World Health Organization.
1268 https://www.who.int/maternal_child_adolescent/documents/trs_886/en/

1269 WHO Secretariat, M. Andersson, B. de Benoist, F. Delange, and J. Zupan. 2007. Prevention
1270 and control of iodine deficiency in pregnant and lactating women and in children less than 2-
1271 years-old: conclusions and recommendations of the technical consultation. Public Health Nutr.
1272 10:1606–1611. https://doi.org/10.1017/S1368980007361004

1273 WHO. 2019. World health statistics 2019: monitoring health for the SDGs, sustainable
1274 development goals. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0
1275 IGO.

1276 WHO. 2020. Vitamin and Mineral Nutrition Information System (VMNIS), Database on Iodine
1277 Deficiency. https://www.who.int/vmnis/database/iodine/en/ Accessed 26 April 2020.

1278 Wilkins, E., L. Wilson, K. Wickramasinghe, P. Bhatnagar, J. Leal, R. Luengo-Fernandez, R.
1279 Burns, M. Rayner, and N. Townsend. 2017. European Cardiovascular Disease Statistics 2017.
1280 European Heart Network, Brussels, Belgium. http://www.ehnheart.org/cvd-statistics/cvd-
1281 statistics-2017.html

Accepted

1282 Yakar S., H. Werner, and C. J. Rosen. 2018. 40 Years of IGF1. Insulin-like growth factors:
1283 actions on the skeleton. J. Mol. Endocrinol. 61:T115-T137.
1284 https://dx.doi.org/10.1530%2FJME-17-0298

1285 Yang, Y., T. A. Churchward-Venne, N. A. Burd, L. Breen, M. A. Tarnopolsky, and S. M.
1286 Phillips. 2012. Myofibrillar protein synthesis following ingestion of soy protein isolate at rest
1287 and after resistance exercise in elderly men. Nutr. Metab. 9:57. https://doi.org/10.1186/1743-
1288 7075-9-57

1289 Zia, A., H. U. Siddiqui, H. Mohiuddin, and S. Gul. 2018. Levelling-off of declining trend of
1290 cardiovascular disease-related mortality in the USA: the challenge to rein in obesity and
1291 diabetes epidemic. Cardiovascular Endocrinology & Metabolism 7:54-55.

1292 Zempleni, J. 2017. Milk exosomes: beyond dietary microRNAs. Genes Nutr. 12:12.
1293 https://doi.org/10.1186/s12263-017-0562-6

1294

1295

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1296 Table 1. Percentage of 3 UK population groups with micronutrient intakes less than the Lower Reference Nutrient Intake (LRNI) and percentage

1297 achievement of the Reference Nutrient Intake (RNI) for vitamin D (Adapted from data in Roberts et al., 2018).

	% with intakes less than the LRNI for:						% RNI
Population	Iron	Calcium	Magnesium	Zinc	Selenium	Iodine	Vitamin D
Males 11-18 years	12	11	27	18	26	14	20
Females 11-18 years	54	22	50	27	45	27	17
Females 19-64 years	27	11	11	8	47	15	21

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1299 Table 2. Effects of vegetarian and vegan relative to omnivore diets on bone mineral density
1300 (BMD) at the lumbar spine, femoral neck and of whole body. (Adapted from data in Iguacel
1301 et al., 2018).

BMD comparison	Mean difference in BMD[3] (g/cm^2)	95% CI[1]	*P*[2]
At the lumbar spine			
Vegetarians + vegans vs. omnivores	-0.032	-0.048, -0.015	<0.05
Vegetarian vs. omnivores	-0.023	-0.035, -0.010	<0.05
Vegans vs. omnivores	-0.070	-0.116, -0.025	<0.05
At the femoral neck			
Vegetarians + vegans vs. omnivores	-0.037	-0.054, -0.020	<0.05
Vegetarian vs. omnivores	-0.025	-0.038, -0.012	<0.05
Vegans vs. omnivores	-0.055	-0.090, -0.021	<0.05
Whole body			
Vegetarians + vegans vs. omnivores	-0.048	-0.080, -0.016	<0.05
Vegetarian vs. omnivores	-0.035	-0.093, 0.022	NS[4]
Vegans vs. omnivores	-0.059	-0.106, -0.012	<0.05

1302 [1]CI, confidence interval, [2]for test if difference was >0, [3]comapred with omnivores, [4]NS, not significant (P>0.05)

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1303 Table 3. Dose-response meta-analyses examining the relative risk (RR) of cardiometabolic
1304 diseases in relation to consumption of dairy foods (Adapted from data in Soedamah-Muthu
1305 and de Goede, 2018).

Disease outcome	Dairy food[1]	RR (95% CI[2])	*P*
Diabetes mellitus	Total dairy	0.97 (0.95-1.00)	NS
	Low fat dairy	0.96 (0.92-1.00)	NS
	Yogurt	0.94 (0.91-0.97)	<0.05
CHD[3]	Total dairy	1.00 (0.98-1.03)	NS
	Milk	1.01 (0.97-1.04)	NS
Stroke	Total dairy	0.98 (0.96-1.01)	NS
	Low fat dairy	0.97 (0.95-0.99)	<0.05
	Full fat dairy	0.96 (0.93-0.99)	<0.05
	Milk	0.92 (0.88-0.97)	<0.05

1306 [1]per increment of 200g/d except yogurt 100g/d, [2]Confidence interval, [3]Coronary heart disease

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1307 Table 4. Changes in blood lipids from baseline to end of 6 weeks intervention when 40 g/d of
1308 dairy fat were provided in 3 types of dairy products (Adapted from data in Feeney et al., 2018).

	Treatment			
Blood lipid (mmol/L)	T1[1]	T2	T3	*P*[2]
Total cholesterol	-0.52	-0.37	-0.15	0.033
HDL-cholesterol	0	-0.07	+0.05	0.284
LDL-cholesterol	-0.45	-0.27	-0.14	0.016
Triacylglycerols	-0.15	-0.05	-0.12	0.386

1309 [1]T1, 120g Cheddar cheese, T2, 120g low fat Cheddar cheese + 21g butter, T3, 49g butter + 30g calcium caseinate
1310 + 500mg calcium (as $CaCO_3$)
1311 [2]for differences between treatments, for controlling factors included in model see original paper

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