

Complex Interactions of Obesity, Dairy Food Intake and Genetics of Lactase

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Abstract

Obesity is a growing global problem associated with multiple diseases, often attributed to a western lifestyle and industrialization. Obesity is associated with low grade inflammation and alterations in the colonic microflora both of which may be instrumental in promoting pathogenesis of diseases. Milk and dairy foods have been suggested to improve weight control which in turn may help reduce risks of complications. In this narrative review the theoretical benefits of dairy foods on obesity are discussed. A search of PubMed, Google Scholar and individual papers spanning the last 21 years are used to retrieve articles dealing with the effects of dairy foods on obesity. Eleven systematic reviews with or without meta-analysis suggest that dairy foods only benefit weight control with short term energy restriction. An important confounder is the role of the genetics of lactase. Ten studies examining the dominant impact of the European gene for lactase persistence suggests that obesity may be related directly or indirectly by allowing more dairy foods intake in conjunction with lactase persistence. However the advancement of obesity into lactase non persistent populations suggests that dairy foods may not be uniquely or universally important to develop obesity. Additional studies are needed to evaluate the complex interactions between weight control, diet and genetics that impact on dairy food consumption and obesity.

Keywords

Obesity, Dairy foods, Lactase distributions, Weight control

Abbreviations

NHANES: National Health Nutrition Survey; NF- κ B: Nuclear Factor kappa-light chain enhancer of activated B cells; TNF α : Tumor Necrosis Factor alpha; IL-6: Interleukin-6; GLP-1: Glucagon Like Peptide 1; CCK: Cholecystokinin; PYY: Peptide Tyrosine Tyrosine; CVD: Cardiovascular Disease; Vitamin D_{1, 25}(OH)₃: 1,25-dihydroxycholecalciferol or Calcitriol the active form of vitamin D; LP: Lactase Persistent Phenotype; LNP: Lactase Non-persistence Phenotype; RCT: Randomized Controlled Trial; WHO: World Health Organization

Introduction

Obesity is a worldwide, progressive problem. While prevalence rates of obesity are high and may be peaking in western societies, there are increasing rates in Asia and South America [1]. Definitions are usually based on the Body Mass Index (BMI) which is the ratio of body weight in kilograms divided by height in meters squared (BMI = kg/m²). Caucasian adults over 18 years are considered overweight with BMI > 25 kg/m² and obesity is defined as BMI \geq 30 kg/m² [2]. Definitions for Asians are somewhat lower (23–27.5 kg/m²) [3]. Recent estimates

of worldwide obesity suggest that about 1.1 billion people are overweight and 0.312 billion are obese. Projections for 2030 suggest that these numbers will double [1, 4]. Of these over 40% occur in children and adolescents [4].

Obesity is intimately associated with multiple medical complications. Metabolic diseases are most often associated with central abdominal obesity and increased waist circumference. Metabolic syndrome with increased hypertension, cardiovascular disease, fatty liver and type 2 diabetes are the most common. However, many others are also present [5, 6]. Several obesity related complications occur earlier and manifest as gastroenterological problems [7]. Many of the diseases associated with obesity potentially share some pathogenic pathways, related to a pro-inflammatory background induced by hormonal changes in obesity [8-12]. It is also thought that changes in the microbiome (largely the intestinal flora) of persons with obesity create a dysbiotic environment (reduced bacterial diversity and richness with loss of beneficial bacteria and emergence of pathobionts) [13]. This feature may also promote inflammation, altered immune responses and altered intestinal barrier functions [13-17]. In addition the microbiome is thought to impact on development of obesity [14, 18]. Dysbiotic alterations in the colonic microbiome are hypothesized as potential facilitators of many diseases [19-23]. Therefore theoretically control of weight gain or improved weight loss could lead to reduced risks for obesity related diseases. The impact of DFs on specific obesity related complications will not be discussed in detail.

Treatment of obesity has then become a worldwide goal. Among treatments, the most logical is the use of diets (restrict energy intake and increase energy expenditure) but difficult to achieve lasting outcome. Among dietary interventions the role of milk and dairy products has been widely studied and results have been controversial. Studies in children and adults have found inverse, neutral or direct effects on parameters of obesity with milk and dairy foods.

In this narrative review the relationships between dairy and obesity are examined. The basic question is whether milk and dairy independently help control weight. In this context, first the rationale why dairy specifically may be helpful in obesity are reviewed. These include anti-inflammatory effects of dairy and the impact they may have on the intestinal microbiome. Secondly, general systematic reviews with or without meta-analyses evaluating the impact of dairy on obesity are reviewed. These studies do not include genetic effects. Thirdly the genetic division of humanity along ability and inability to digest the milk disaccharide lactose is examined as a possible modifier of outcome due to two attributes. These include the quantitative difference in dairy consumption between lactase persistent (dominant trait with retention of intestinal lactase into adulthood) and non-persistent peoples (recessive trait with loss of intestinal lactase in adulthood) and fermentation in the colon of excess lactose by the latter group. This takes into consideration the increasing use of Mendelian randomization to reduce confounding and possible reverse causation effects due to the genetic population differences [24].

Methods

A nonsystematic but focused literature search was undertaken in Medline, PubMed and Google Scholar (January 1996 to March 2018). The search included publications in English, related to effects of dairy foods on the intestinal microbiome and on inflammation a broad range of combination of terms were used: obesity, body mass index, waist circumference, weight control and effects of milk, dairy products or dairy foods consumption and lactase distributions or lactase persistence. Personal archived references were also included in the search. Preference was given to include systematic reviews, meta-analyses with or without Mendelian randomization. However, observational studies and randomized controlled trials were included where appropriate. This style of narrative review has been previously published [25].

Body of Review

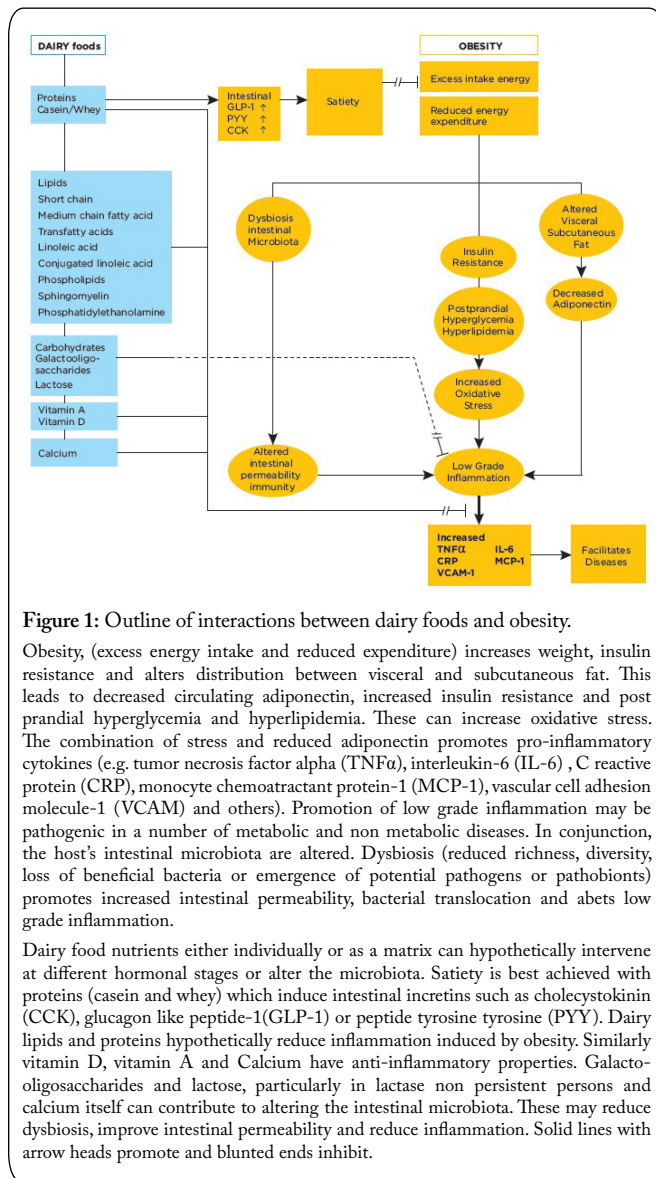
Potential benefits of dairy foods in weight control

There are several mechanisms related to milk and dairy foods which may promote weight reduction and counteract harmful effects associated with obesity. Milk contains nutrients which reduce hunger by enhancing satiety, individual nutrients are considered to possess anti-inflammatory effects and dairy foods can impact on the microbiome by different nutrients. Hypothetical and theoretical effects of obesity leading to inflammatory response and potential interventions by nutrients in dairy products are shown in figure 1.

Overeating depends on an interplay between hormones which promote or reduce hunger. Food induces incretins, which stimulate glucose control. Glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK) and peptide tyrosine tyrosine (PYY) promote satiety and reduce hunger. Of the three main ingested nutrients, proteins induce satiety the best [26]. Milk and yogurt consumed before or within meals is associated with higher levels of GLP-1 and PYY [27, 28]. Of milk proteins, casein (80% of milk protein) is slowly digested, due to precipitation by acid, hence a slower effect on satiety. However, its impact is longer. Whey (20% of milk protein) is a fast protein with rapid onset of action but shorter impact on satiety [29]. Proteins also down regulate inflammation [30]. Yogurt also slows gastric emptying possibly prolonging effect on satiety [31]. These studies suggest that milk and dairy foods achieve satiety with reduced food intake although results are not consistent.

Anti-inflammatory nutrients in milk and dairy

In the last decade the role of high or regular dairy fat intake in cardiovascular disease (CVD) and overweight has been challenged. There is no clear evidence that CVD is increased and some studies suggest that obesity and metabolic syndrome may be averted [32]. The hypothesis that total dairy food matrix rather than individual nutrients be considered when evaluating outcomes has emerged [33]. Nevertheless, individual fats in dairy foods, have been found to have anti-inflammatory actions [34].



There are conflicting reports on dairy effects on biomarkers of inflammation in clinical studies. Some studies report inverse associations with biomarkers [35, 36]. Others, including a meta-analysis failed to show more than minimal clinical effects on biomarkers [37, 38]. Further studies will be needed to establish clear benefit of dairy products in counteracting pro-inflammatory events associated with obesity.

A number of micronutrients and vitamins may also contribute to an anti-inflammatory effect by dairy. Among these vitamins A and D are considered. *In vitro* all-trans-retinoic acid suppresses NF- κ B signaling [39]. Also *in vitro* it exerts a dampening effect in the presence of endotoxin stimulation as well as in a mouse model [40]. There are no clinical studies however, confirming these effects [30].

In western societies the addition of vitamin D to milk and some dairy foods may also contribute to anti-inflammatory effects [41-43]. However, there is conflicting evidence, suggesting that deficiency of vitamin D may be associated with promotion of low grade inflammation [44]. Higher doses of vitamin D however, may produce variable outcome

without clear evidence of downgrading [30]. Finally calcium as well as magnesium present in milk have also been found to be modestly and inversely associated with some markers of inflammation [30].

At low serum vitamin D levels there is an inverse association with BMI [45]. The exact mechanism of the relationship is not clear and is extensively reviewed by Dix et al. [46]. Part of the controversy stems from different effect of vitamin D on adipocytes *in vivo* or *in vitro* as well as variability of impact from humans, mouse models or cell cultures.

In mouse cell lines vitamin D inhibits adipogenesis. However, in human cell cultures vitamin D enhances adipocyte maturation and increases lipid storage. Similar discrepancies are noted in observational and interventional studies. As a result, Dix et al. conclude that it has not been established whether low vitamin D predicts lean or obese body habitus and whether deficiency is a consequence of obesity due to increased adipocyte storage and reduced release [46].

It also has been difficult to determine whether effects on fat tissue are due to interactions with calcium [46]. At least 3 hypotheses have been suggested to be relevant for interactions with calcium in obesity. First, calcium alters the lipid profile with increased high density (protector) to low density (detrimental) cholesterol ratio. The putative mechanism is the interaction of calcium with fats forming soaps decreasing fat absorption. A second possible interaction is the binding of calcium with bile acids and preventing their reabsorption. As a result more cholesterol is converted toward bile acid synthesis [47]. Thirdly, Zemel et al. put forth a hypothesis suggesting that in the presence of low calcium, parathyroid hormone levels and vitamin D_{1, 25}(OH)₃ are increased. The increased vitamin D enhances intracellular calcium concentrations. This in turn increases lipogenesis and inhibits lipolysis [48-50]. Addition then of calcium in the range of 1-1.2 g/d to the diet, may help by inhibiting the effect of intracellular calcium and increasing thermogenesis. The role of dietary calcium remains controversial and it is suggested that better effects are achieved when initial calcium intake is modest (≤ 700 mg/day) and accompanied by energy restriction [50].

Vitamin D deficiency through alteration of the microbiome can lead to vitamin B complex deficiencies inducing a hyperadrenergic state which increases cardiovascular disease risks [44].

Calcium may alter the intestinal microbiome as well and promote the expansion of lactobacilli [51]. These bacteria may reduce risk of obesity related type 2 diabetes [52]. Calcium also reduced endotoxin translocations and improved intestinal barrier function [51].

Other nutrients may also affect the microbiome. During lactation mother's milk contains many prebiotic galacto-oligosaccharides which protect the neonate from pathogens and compensate for prematurity of intestinal development [53-55]. In under nourished children where the intestinal disaccharide levels may be deficient, lactose containing milk may contribute to nutrition [56].

In adults about a third of the world's population has the dominant genetic trait allowing consumption of fresh milk without incurring symptoms even with ingestion of large amounts in single intakes (lactase persistence) [57]. In the rest, quantities of lactose which overwhelm residual intestinal lactase are metabolized by intestinal bacteria and may cause intestinal symptoms [57, 58]. These adults are lactase non-persistent and have the wild type or recessive form of the gene for intestinal lactase [59, 60]. Regular consumption of lactose present over time can result in colonic bacterial adaptation through altered microbial flora which reduces symptoms and may impact on diseases affected by dysbiosis [61-64].

In summary milk and dairy foods have a potential to prevent weight gain through providing adequate satiety. In addition obesity related consequences may be counteracted by reducing the pro-inflammatory effects of acquired fat cell mass and help maintain a normal microbiome in the intestinal tract. Nevertheless clinical studies are conflicting.

Obesity and consumption of milk and dairy foods: general summary reviews

The effects of dairy on body weight parameters is evaluated through review of the outcomes of systematic reviews with or without meta-analyses in children, adolescents and adults. Table 1 lists 11 such studies. Five studies evaluated children or adolescents [65-75]. Two of these studies included adults analyzed separately as well [66, 70].

Early prevention of obesity in childhood could have far reaching effects in controlling weight.

In the systematic reviews of children, however, earlier reports showed largely neutral dairy effects [66, 67, 69]. For example in the review of Spence the summary results of 47 observational studies revealed that 53% of all studies failed to show improvement in weight, 42% reported improved weight control and 3.6% showed increased weight [67]. The more recent meta-analysis and review by Dror found that DFs may be modestly protective against obesity in adolescents only [69].

Two subsequent observational studies however, did show inverse effects of highest dairy intake with obesity in children [70, 71].

A number of individual studies also favored a beneficial effect of dairy. Replacement of sugar containing drinks with equivalent amounts of milk prevented weight gain that could be observed with the consumption of sugar drinks [76]. Consumption of yogurt, higher calcium and vitamin D were associated with a lower risk of body fat in the NHANES study [77]. However, a more recent, randomized controlled trial on milk and dietary calcium in adolescent females compared to controls failed to find any effect on weight gain [78].

Table 1 contains 8 reports on the effects of dairy on obesity in adults [65, 66, 68, 70, 72-75]. Of these as stated before 2 included data on children as well [66, 70]. In a large systematic review of randomized controlled trials by Lanou the majority of 49 studies reported neutral effects and only 5 suggested benefit of DFs for weight loss [65].

A similar outcome of neutrality was reported by Schwingshackl in a meta-analysis of 22 cohort studies. Only analysis of yogurt showed a significant benefit for weight loss [68]. Alternatively Wang et al. showed a modest benefit of total dairy products or milk in reducing risk of obesity [70]. However, 4 published meta-analyses found that dairy may improve weight loss and attenuation of lean mass loss only when energy restriction is included [72-75]. Further this effect is limited to short periods less than 1 year [73]. Also the beneficial effects of dairy together with energy restriction for weight loss may be less relevant for males since the meta-analysis of 27 randomized clinical trials by Stonehouse included 90% women [74]. The most recent meta-analyses of 37 randomized controlled trials by Geng et al. showed that without energy restriction body weight increased with dairy [75].

There is therefore inconsistent reporting on the effects of dairy on obesity in children, and further randomized controlled trials may help clarify the controversy. However, in adults and adolescents dairy may help in short term to control weight together with energy restriction. As a result there is no strong evidence that dairy independently promote weight control.

Effects of lactose digestion status on dairy food, obesity interactions

In the last 50 years it has been established that the 2 phenotypes of lactase persistence and lactase non-persistence are dependent to date on 5 known principal polymorphisms [59, 60, 79, 80]. As a result of a dominant mutation in the promoter region of the lactase gene on chromosome 2 [81], 1/3 of the world's population retain intestinal lactase and the ability to digest the disaccharide lactose. The remaining 2/3 lose intestinal lactase and can no longer digest large amounts of lactose. This loss results in development of gastrointestinal symptoms when large amounts of lactose are consumed in a single meal. Perhaps as a result of this altered digestion status or because of geographic and cultural differences, lactase non-persistent people consume less dairy [82-85]. As well extra ingested lactose is fermented in the colon by bacterial action [86]. World lactase distributions may impact on epidemiology of some non-communicable diseases [84], particularly those attributed to western lifestyles, which promote cancers and autoimmune diseases. Among "western" type diseases obesity is considered to have originated initially from western societies.

Earlier studies from Brazil [87], Korea [88, 89], and Japan [90] where the majority of the population is lactase non-persistent suggest reduced risks of obesity with dairy products. However, a study from Hong Kong where the lactase non-persistent frequency is above 90%, reported that in adolescents, while milk and dairy consumption correlated positively with social status, it did not correlate with BMI [91].

Other publications do not support a specific deleterious effect of lactase persistence or a protective effect of lactase non-persistence against obesity. In fact the dominant lactase persistence genotype was found to be protective for obesity [92]. A study from Luxembourg reported in an observational format a protective effect of total dairy food intake, despite whole fat content against obesity and cardiovascular disease [93]. In

Table 1: Systematic reviews or meta-analyses of possible impact of dairy products on weight.

Summary and outline of published systematic reviews with or without meta-analyses evaluating dairy food consumption for weight control. There were overlaps in studies among publications. The number of participants were in the range of 234,954 children and 323,790 adults in systematic reviews, 46,011 children in meta-analyzed cohort study, 4262 in three meta-analyzed randomized controlled trials in adults. In the latest study by Geng, 184,802 participants were included. In 2 additional studies the total numbers of participants was not given.

Author Year [References]	Number of studies in review	Types of studies	Exposure to Type of Nutrients	Outcome effects on Body Weight and Composition By included studies
Lanou 2008 [65]	49 System Rev	Randomized Controlled Trials Range of Follow up 2-12 years Adults	Milk, Dairy products, Calcium	41 neutral, 5 weight loss, 1 slow rate gain 2 weight gain
Louie 2011 [66]	19 System Rev	Prospective cohort 10 Children/adolescent 9 Adult	Variety of Dairy Products	3/10 and 5/9 studies showed protective effect against weight gain
Spence 2011 [67]	47 System Rev	Children 23 cross sectional (31 outcomes) 13 prospective 11 randomized	Dairy Products or Calcium	18 benefit, 13 neutral 8 neutral, 4 benefit, 1 gain 9 neutral, 1 benefit, 1 gain
Schwingshackl 2016 [68]	22 Met-An	Adult Cohort studies	Various Dairy Products	5 Met-An for Yogurt only Showed benefit for weight control Rest neutral
Dror 2014 [69]	36 System Rev 22 were included in Met-An	Pre School, School-Age and Adolescents Cross sectional Observational Interventional Range of Follow up 0.5-13 years	Milk Dairy Products	BMI, WC, Adipose tissue Final analysis neutral effects were found in early to middle childhood and modest protection in adolescents
Wang 2016 [70]	24 Met-An	Cross Sectional case-control 10 Children 12 Adult	Total Dairy a. Product Intake or b. Milk Intake	Risk of obesity decreased with highest DF intake In both children and adults OR 1a. 0.54 (95% CI 0.38 – 0.77) 1b. 0.77 (95% CI 0.68 – 0.87) 2a. 0.75 (95% CI 0.69 – 0.81) 2b. 0.77 (95% CI 0.68 – 0.87)
Lu 2016 [71]	10 Met-An	Children , Cohort	Dairy Foods Intake	OR highest vs. lowest DF intake Protects against obesity 0.62 (95% CI, 0.49-0.80)
Abargouie 2012 [72]	14 Met-An	Adult, Randomized Controlled Trials	Dairy Food Intake	Standard mean difference of parameters. Significant only with energy restriction BW- 0.61 kg (95% CI -1.29 – 0.07) p = 0.08 FM- 0.72 (95% CI -1.29 – -0.14) p < 0.01 LM- 0.58 (95% CI 0.18 – 0.99) p < 0.01 WC- 2.19 (95% CI -1.9 – -0.6) p < 0.001
Chen 2012 [73]	29 Met-An	Adult, Randomized Control Trials Duration 1-36 months	Dairy Food Intake	Standard mean difference of parameters BW-0.45 kg (95% CI -0.79 – -0.11) Largely neutral except with energy restriction 22/29 studies for short term(<1 year)
Stonehouse 2016 [74]	27 Met-An	Adult, Randomized Control Trial (90% female) All with energy restriction	Dairy Food Intake 2-4 servings/day	Energy restriction showed greater benefit with DFs for weight loss and prevented loss of lean mass. Standard mean difference of parameters BW-1.16 kg (95% CI -1.66 – -0.66) p < 0.001 Body FM-1.49 (95% CI -2.06 – -0.92) p < 0.001
Geng 2018 [75]	37 Met-An	Adults Randomized Control Trials	16 studies with energy restriction 21 without Dairy Products included low and high fat milks and other foods including cheese	High Dairy no energy restriction: increased BW, LM. Decreased BF, WC overall. In subanalysis no energy restriction Increased BW In subanalysis with energy restriction High Dairy Decreased BW, BF, and WC

System Rev: systematic review, **Met-An** = meta-analysis, **OR:** odds ratio, **BW:** body weight, **BF:** body fat, **FM:** fat mass, **LM:** lean mass and **WC:** waist circumference.

addition total dairy consumption was associated with protection against weight gain in elderly and middle aged women in a large prospective Women's Health Study from the United States, again with the majority being lactase persistent [94].

Nevertheless, examination of the global rates of obesity compared with lactase distributions tend to show inverse relationships especially among males [95, 96]. This relationship with lactase distributions enforces an evaluation with dairy and begs the question how lactose digestion status impacts on dairy consumption and obesity.

The potential role of genetic attributes to outcomes requires methodology which takes into account inherent biases of confounding and the possibility of reverse causation (where the outcome affects exposure). One caveat is there should be no horizontal pleiotropy, where the genetic trait affects the outcome independent of exposure [97]. Table 2 outlines 10 studies which have examined the association between lactase persistence, features of obesity and dairy intake [98-107]. Three studies only evaluated relationship between lactase persistence status and obesity [98, 102, 106]. Seven of the studies also included dairy consumption [99-101, 103-105, 107]. Three of the 10 studies were restricted to children or young adults [102, 103, 106]. Three studies carried out Mendelian randomization methods [104, 105, 107]. All studies evaluated the north European polymorphism C/T-13910 as an indicator of lactase persistence (TT, CT dominant trait) or lactase non persistence (CC recessive trait).

Of the studies which examined lactase persistence only, Manco et al. and Kettunen et al. reported positive associations of lactase persistence with BMI in young or older adults [98, 106] while Albuquerque found that only central abdominal obesity in lactase persistent children were associated significantly [102]. These studies suggest that lactase persistence may be independently associated with obesity and need to be confirmed.

In addition to lactase persistence associated with BMI, 2 studies concluded that dairy consumption was also increased in lactase persistent persons [99, 101]. The reports by Corella et al. and by Malek et al. also found increased lactose intake to be also associated with obesity in addition to lactase persistence [100, 103]. In the study by Corella et al. men were more affected than females [100].

Among the 3 studies using Mendelian randomization Hartwig et al. found an important difference in outcome between the use of Mendelian randomization and conventional analysis. The significant decrease in weight with 1 dl/day intake of milk, was abrogated when the former method was applied [105]. In the large Danish study by Bergholdt et al. the hypothesized negative association of dairy intake with overweight-obesity was not found [104]. In the most recent and largest single study using Mendelian randomization of multiple sources genetics were used as an instrumental variable as a proxy for increased dairy consumption [107]. In this analysis both lactase persistence and increased dairy consumption were linked to obesity (BMI) and the authors concluded that dairy intake was causative of obesity [107].

These comparisons suggest that generally lactase persistence may be associated with increased BMI and is associated with increased dairy consumption. These studies lead to 2 possible problems. First if lactase persistence is independently associated with obesity (as per refs 98, 102, 106) then the caveat that no horizontal pleiotropy (ie. lactase persistence increases obesity independent of exposure dairy) should exist may be violated in this kind of analysis of genetic confounding. It is difficult to separate the impact of genetics which also increases dairy consumption and obesity. Secondly, there is little information on the interaction with other LCT polymorphisms [59, 60, 79, 80] to independently verify the association with lactase persistence status associated with other polymorphisms. This may be quite relevant if all other dominant lactase persistence genes were or were not also linked with obesity independent of dairy consumption.

Summary and Conclusions

Obesity is a growing global problem with multifactorial causes. The treatment of this condition becomes a primary target because it is linked with many medical illnesses and it is suggested that improvement in obesity is associated with improved health. Since, central causation, depends on increased energy intake part of treatment plans include diet. In this context a recurrent topic of research in the last 2-3 decades concerned the unique role of dairy foods, particularly since these are considered to be beneficial in general [108]. In obesity control the role played by dairy remains somewhat blurred.

Milk and dairy foods have theoretical attributes which could possibly counteract obesity induced pathogenic pathways. In addition, recent reports suggest that different dairy products (Matrix effects [33]) may have different effects on obesity [109].

This review suggests that evaluating the impact of dairy on obesity is somewhat affected by incorporating the effects of lactase genetics. Both methods find that energy restriction together with dairy may be more effective than without dairy. However, when lactase status is incorporated in analyses and particularly using Mendelian randomization in general any benefits of dairy are abrogated. It is not clear from the literature whether the European dominant gene for lactase persistence independently increases BMI. This association if confirmed, could constitute a horizontal pleiotropic bias [97]. The association with lactase persistence also increases dairy consumption, making it difficult to separate the effects of each. The most recent study uses the lactase persistence as an instrumental variable, as proxy for increased dairy consumption and concludes that the observed obesity associated with lactase persistence is due to dairy.

There are two outstanding questions. The first is the failure to relate obesity in lactase non persistence populations with dairy consumption as was suggested in Lin et al. study from Hong Kong [91]. Second there are few if any studies evaluating dairy and lactase persistence with any of the other lactase polymorphisms to determine the effect of this dominant genetic trait on obesity [59, 60, 79, 80]. As such

Table 2: Studies evaluating the effects of lactase persistence gene on parameters of obesity and dairy product (DF) intakes.

Author year [References]	No. of patients	Exposure; LCT with or without DF	Anthropometric Measurements	Outcome
Kettunen 2010 [98]	31720 (9 populations in Europe)	LP status	BMI	Highly significant Association of LP status with BMI $p \leq 0.0001$
Almon 2012 [99]	551	LP DF questionnaire	BMI	BMI Associated with LP
Corella 2013 [100]	940	16.3% TT 38% CC 45.7% CT DF assessed	Weight, BMI, WC	TT associated with markers of obesity OR 1.38 (1.05-1.81) DF intake lower only in CC women
Lamri 2013 [101]	3575	78.5% TT, CT DF assessed	BMI	Higher BMI by 0.3 kg when DF intake is medium or high
Albuquerque 2013 [102]	580 children	TT and CT (genetics and obesity only)	Abdominal Obesity	Obesity associated with LP higher OR 1.65 (1.04 - 2.6)
Malek 2013 [103]	296 children	LP Lactose consumption	BMI, FMI, WC	Markers of Obesity significant BMI $p = 0.043$ FMI $p = 0.043$ WC $p = 0.008$
Bergholdt 2015 [104]	97,811	TT/TC vs CC Mendelian Randomization Compared with standard observational model DF intake	Markers of Obesity as defined by overweight	Obesity associated OR 1.06 (1-1.12, $p = 0.04$) High DF intake not associated with low risk obesity
Hartwig 2016 [105]	1982	LP Mendelian Randomization DF intake	BMI	Overweight obesity 1.09 (1.02 – 1.17) LP; Higher BMI by 0.017 0.07-0.27 kg/m ² DF inversely associated with BMI but not supported by MR method
Manco 2017 [106]	447 young adults	TT% 16.1 CC% 35.8 CT% 48.1	BMI %fat Weight	Logistic regression showed significant associations between LP and BMI %fat, Weight and obesity risk
Huang 2018 [107] (MRDCWGroup)	184802	LP and DF Mendelian Randomization with genetics as instrumental variable	BMI	Associations of TT,TC with DF intake, TT,TC higher BMI, BMI higher DF intake DF in LP causes Obesity

LCT: lactase gene, **TT:** dominant lactase persistent (LP), **TC:** heterozygous and **CC:** recessive lactase non persistent (European C/T-13910, rs4988235). **BMI:** body mass index, **FMI:** fat mass index, **WC:** waist circumference, **OR:** odds ratio, **DF:** dairy foods.

the specific role of dairy in weight control is still unclear but is suspected to be at best modest either way. Nevertheless it may be more valid to examine role of dairy separately in either lactase persistent or lactase non persistent populations.

Conflict of Interest Statement

The author declares that I have no competing interests.

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Synopsis

Obesity is emerging as a far reaching global problem which portends and facilitates numerous medical problems. It is suggested that weight control could reduce burden of chronic diseases. In this paradigm successful treatment with diet would be ideal. Dairy foods have been postulated to help reduce obesity related parameters. However, outcome is conflicted due to a number of intervening factors. This narrative review examines three questions. Why are dairy foods considered unique to control obesity, what evidence is there that dairy foods independent of energy restriction improve weight control and what is the impact of the genetic dichotomy that determines lactose digestion on outcome of dairy foods on obesity. The review suggests theoretical aspects of dairy foods may improve satiety and have anti-inflammatory effects on the host and on the host's microbiome which could counteract potential disease producing effects of obesity. A literature review suggests that

dairy foods help with weight control only in the context of energy restriction but exert neutral effects otherwise. Dairy foods therefore are somewhat unique because outcome with energy restriction may be better than with other nutrients. When genetics of lactase are incorporated and observational studies are compared with Mendelian randomization methods the apparent benefit of dairy foods is blurred. However the existence of possible horizontal pleiotropy in that lactase persistence may be independently associated with obesity increases the complexity of determining specifically the role of dairy foods in obesity. Additional studies are needed to work out the complex interactions.

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