

Review

## Physiological Impact of Milk on Multiple Health Outcomes in Human

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### Abstract

Milk is best known as a nutrient-rich fluid produced by the mammary glands of mammals, designed primarily to feed young. In the human diet, cow milk is most prevalent, but milk of other mammals and plant milk are common too. This study aims to investigate milk's nutritional value in various age groups and review opposing evidence of its effect on cardiovascular diseases in adults. It is a literature-based strategy to synthesize information from observational and meta-analytic studies. The milk content—macronutrients, vitamins, minerals—was compared to its role in maintaining growth, development, and well-being. In addition, evidence was reviewed on milk intake during adulthood and its link to cardiovascular wellness to assess risk relationships. Milk is rich in good-quality proteins, essential fatty acids, vitamins (A, D, B12), and minerals (calcium, phosphorus), beneficial for immune function, bone health, hydration, and weight control. Infants and children particularly gain advantage from its complete nutrient profile, while in adults, it contributes to muscle repair and cardiovascular health. Evidence regarding milk's role in cardiovascular disease (CVD) is contradictory. Some find a protective effect, while others report increased risk. Interestingly,



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a meta-analysis of prospective trials found that a daily consumption of 200 mL of milk was associated with a statistically significant reduction of CVD risk, even when whole milk was consumed. Milk remains an integral part of human nutrition due to its high nutrient content. Nonetheless, incongruent outcomes of its contribution to cardiovascular morbidity necessitate personalized dietary instructions. Further work should elucidate mechanisms for incongruent observations and provide concrete recommendations for milk intake for different ages and diseases.

### **Keywords**

Milk consumption; age groups; osteoporosis; dietary limitations; metabolic function; cardiovascular disease; nutrient-dense food

## **1. Introduction**

Milk has been among the most complete and accessible dietary elements for many years. For thousands of years, milk has been a priority in the diet at all life stages- from infancy to adulthood- as it provides the necessary active agents that support growth and development and help preserve health. Milk plays a crucial role in our diet throughout our lives. It contains essential, vitamins, and minerals that help our bodies work well. This is why experts often tell us to drink milk. For babies, milk is their main food and the most crucial thing they eat. A mother's breast milk is just right for what a baby needs. It has the perfect mix of nutrients for the first few months when babies grow and change. The blend of proteins, fats, carbs, vitamins, and minerals in breast milk also boosts a baby's immune system. This helps keep the baby healthy and protects it from getting sick [1]. When breastfeeding is impossible, formula milk replaces the mother's milk, supplemented with all the nutritional factors present in the maternal milk to the maximum possible extent. Milk can still be an instrumental of a child's diet as they grew. This food is rich in calcium and vitamin D, essential for the normal development of bones and teeth [2]. These elements should be sufficiently ingested, mainly when children and teenagers are in their growth period, since the rate of growth of their bones is higher. In addition, milk also favors muscles and development in general, since it is rich in protein. In addition, milk consumption among school-going children assists in the development of the brain, energizes the body, and improves physiological health; it thus also has a significant role in sustaining a healthy lifestyle [2].

Milk remains an essential supplement in this category even later in adulthood. It offers substances required by the bones, especially for women due to high demand occasioned by hormonal changes upon menopause. The high quality of protein in milk supports muscle maintenance and the control of diseases related to muscle wasting that occurs with the natural loss of muscle mass due to aging. It is an even better source of B vitamins, especially energy-related B vitamins, and for maintaining the health of the nervous system [3]. Thus, a few bioactive compounds, along with the favorable nutrient profile of milk and its products, have been associated with a reduced risk of cardiovascular disease, type 2 diabetes, and hypertension [4].

The relationship between adult milk consumption and cardiovascular health remains a subject of ongoing debate due to contradictory findings in observational studies and meta-analyses. While

some trials suggest that milk intake may confer a protective effect against cardiovascular disease (CVD) and reduce the risk of all-cause mortality, others indicate potential risks associated with its consumption. A comprehensive meta-analysis of prospective trials revealed that the intake of 200 mL of milk per day was associated with a statistically significant reduction in the risk of CVD. This protective effect was observed irrespective of the fat content of whole milk, challenging the traditional concerns regarding dairy fats and their impact on cardiovascular health. These findings underscore the complexity of milk's role in human nutrition and highlight the need for further research to reconcile these divergent outcomes and provide more explicit dietary guidance.

The systematic review by Soedamah-Muthu et al. [5]. likely represents a foundational analysis of the relationship between milk consumption and health outcomes such as cardiovascular disease (CVD), stroke, and mortality. However, this review appears to have limitations that necessitated including an additional study from 1984 in the analysis. Specifically, the decision to exclude certain studies in their meta-analysis (due to a lack of specific data on milk intake or their focus on dairy products broadly) might have impacted the robustness or generalizability of their findings. By highlighting the gaps or limitations in the earlier meta-analysis—such as excluded studies, methodological constraints, or insufficient focus on specific variables (e.g., age, BMI, total energy intake, physical activity)—the rationale for conducting the current study becomes clearer [2].

Milk contributes some nutritional benefits among elderly individuals, many of which can help to offset nutritional problems common at this stage in their lives [3]. As aging goes on, the body's capability of absorbing and utilizing several nutrients is reduced; hence, these increase the chance of deficiencies. Milk is a focused source of such nutrients, which is very important in preventing nutrient deficiency. Calcium and vitamin D remain very essential to maintain the health of your bones, reduce the risk of fractures, and prevent osteoporosis which is common among older adults [6]. In addition, milk protein can be beneficial in maintaining the muscles that are very important to reduce the symptoms of sarcopenia, the condition of losing muscle mass and strength.

### **1.1 Milk Synthesis and Composition**

Milk is a complicated biological liquid that is made up of water, proteins, fats, carbohydrates (primarily lactose), vitamins, and minerals. Water is the primary element of milk, accounting for 87%, with various dissolved and non-dissolved components following. Milk proteins consist primarily of casein and whey, with casein accounting for 80% and whey making up the remaining 20%. They have many crucial amino acids and are very easy to digest. Approximately 3-5% of its makeup consists of fat in the shape of globules that provide essential fatty acids and vitamins (A, D, E, K) derived from milk. Lactose, a basic sugar present in milk, is rich in calcium and acts as a quick energy source. Milk delivers numerous minerals such as calcium, potassium, and phosphorus, along with a substantial amount of B12, riboflavin, vitamin D, and more. The alveolar cells produce these compounds, which are released to create human milk in the mammary gland. "Human milk is specially designed to meet the nutritional needs of infants, which are essential for optimal growth and development." Lactose is generated by the enzyme lactase synthase, which facilitates this reaction [4]. In alveolar cells, primarily casein, milk proteins are produced at the rough endoplasmic reticulum and are packaged into secretory vesicles by the Golgi apparatus. Triglycerides are formed from circulating fatty acids (derived from diet or adipose tissue) and glucose, and are then stored

within cells in the smooth endoplasmic reticulum. These secretory elements are discharged into the alveolar lumen, where they combine with water and electrolytes to create milk after exocytosis.

The production and release of milk are regulated by hormones like prolactin, which promotes milk creation, while oxytocin facilitates the contractions needed to release it. Human babies assimilate human milk more easily than other milk varieties. This is because of the enzymes that help break down milk's components, along with proteins that the baby's intestines absorb more easily. Alternative types of milk, such as cow's milk, have a different nutritional profile that is not as suitable for human infants. Human milk contains many immune elements, such as antibodies and white blood cells, that help protect infants from infections. These immune elements are missing in other types of milk. Human milk contains live bacteria that support the development of a healthy gut microbiome in babies. These microorganisms are essential for digestion, immune health, and overall wellness. Various types of milk do not contain live bacteria. These differences highlight the importance of breastfeeding for infants, as human milk provides ideal nourishment and protection for optimal growth and development.

### 1.1.1 General Significance of Milk in Diet

As individuals move through the phases of life, milk remains an integral part of their nutrition. Milk promotes skeletal growth and cognitive development in children and adolescents, while it helps adults and the elderly maintain muscle mass and prevent illnesses like osteoporosis, sarcopenia, and hypertension. Despite its numerous physiological benefits, the health consequences of regular milk consumption are a source of scholarly controversy. The broad definition of "dairy products" in the literature that is currently available, which frequently encompasses cheese, yogurt, and other fermented or processed foods, dilutes insights unique to milk. Furthermore, many studies do not disaggregate data by life stage, gender, or geographic region, limiting the ability to produce exact, tailored dietary recommendations. There is also minimal understanding of how the bioactive components of milk, including casein variations, milk-derived exosomes, and peptides, interact with individual metabolic profiles or contribute to long-term health programming.

Given these shortcomings, the current study will conduct a targeted meta-analysis and literature review to critically analyze the impact of milk consumption on health outcomes in newborns and adults. Through the separation of milk-specific data and the consideration of essential confounders like age, body mass index (BMI), total energy intake (TEI), and physical activity (PA), this study aims to elucidate the connection between milk consumption and outcomes like mortality, metabolic control, and cardiovascular health. The ultimate goal is to support the development of more complicated, evidence-based dietary guidelines that take into account the intricate function that milk plays in human nutrition.

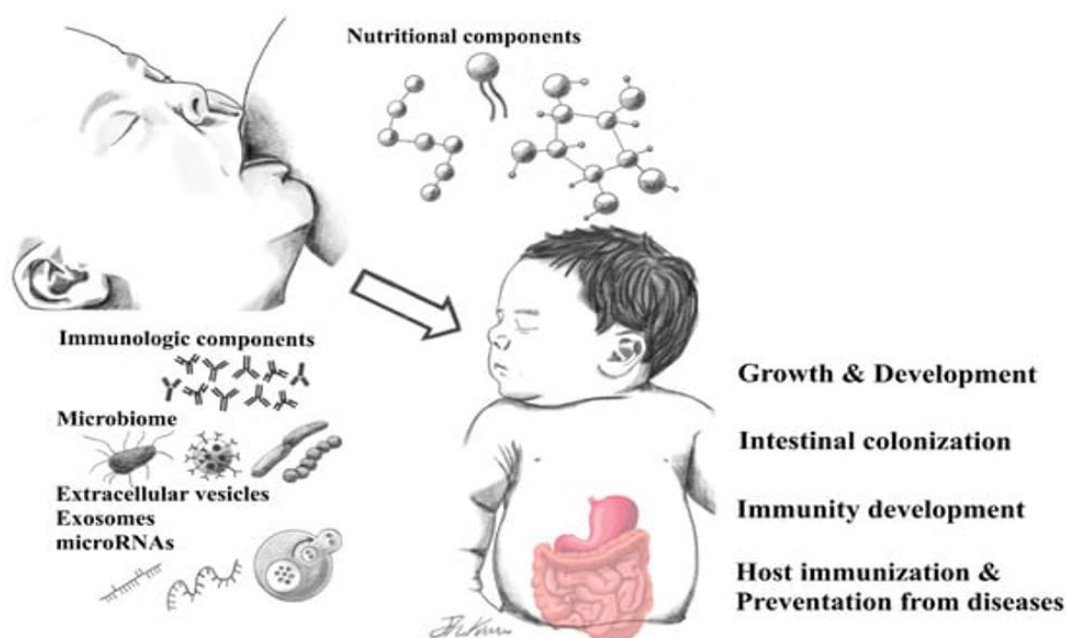
### 1.2 Significance of Milk in Infants

Milk and dairy products are vital sources of various essential nutrients, some especially important at specific life stages [3]. It is now understood that milk protein can activate insulin-like growth factor-1 (IGF-1), which is required for longitudinal bone growth and bone mass acquisition in young children, lowering the risk of stunting. The knowledge that certain foods include micro-components that may help maintain and prevent disease is growing among consumers. These beneficial food

ingredients, which include EPA, DHA, and CLA, are found in milk fat. The advantages of including milk in a child's diet have been recognized for many years. For instance, a 1926 report from the UK Medical Research Council found that providing an extra 568 mL/day of milk to boys in a children's residential home resulted in significant growth improvements [3]. This finding later influenced UK nutrition policy to promote milk consumption among children. Recently, there has been a growing emphasis on childhood nutrition, with increasing evidence showing that diets during this stage can affect long-term health [7]. It is well-established that childhood undernutrition can lead to reduced linear growth (stunting), slower cognitive development in the short term, and, in adulthood, issues like hyperglycaemia, hypertension, high cholesterol, and obesity.

### 1.2.1 Role of Breast Milk

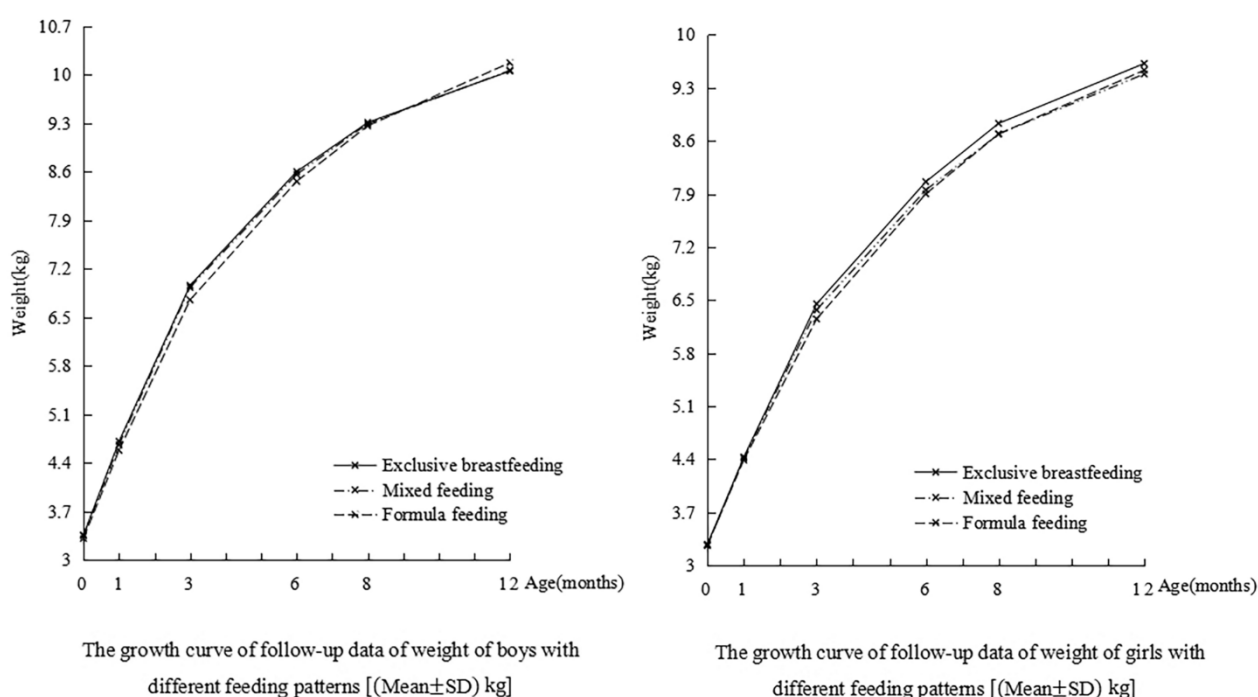
Human breast milk supplies essential nutrients and bioactive components crucial for supporting an infant's growth and immune system development. Differences in milk composition, influenced by demographic factors, genetics, maternal lifestyle, and environmental exposures, can impact infant health in both beneficial and harmful ways. Breastfeeding is linked to better health outcomes for infants, including enhanced immune function, fewer cases of gastrointestinal illness, and lower mortality rates compared to formula-fed infants [8]. Beyond basic nutrition, breast milk also provides beneficial bacteria that help protect against harmful pathogens and encourage the growth of healthy gut microbes as shown in Figure 1 [9]. Breastfed infants are reported to have a dynamic gut microbiome and have reduced incidences of certain diseases. In addition to macro- and micronutrients and bioactive compounds, human breast milk contains many bacterial species [10]. Breast milk is crucial in introducing beneficial bacteria to the infant's gut after birth. Recognition of the human milk microbiome as a key contributor to infant health has led to extensive research to understand its functions. These include the production of antimicrobial substances, blocking harmful bacteria from attaching to the intestinal lining, and boosting the production of intestinal mucin.



**Figure 1** Significance of breast milk [3].

### 1.2.2 Nutritional Significance

A wide variety of proteins are present in human milk, which adds to its unique qualities. Many of these proteins are broken down to provide newborns with the necessary amino acids for their rapid growth. A few proteins that help in milk digestion and absorption are bile salt-stimulated lipase, amylase,  $\beta$ -casein, lactoferrin, haptocorrin, and  $\alpha$ 1-antitrypsin. Immunoglobulins,  $\kappa$ -casein, lysozyme, lactoferrin, haptocorrin,  $\alpha$ -lactalbumin, and lactoperoxidase are a few examples of proteins having antimicrobial qualities that are resistant to digestion in the gastrointestinal system and aid in shielding breastfed children from pathogenic bacteria and viruses. The association of milk consumption and child growth in Figure 2, shows how milk plays a crucial role in development of children. Moreover, the proteins in human milk may encourage the development of good bacteria like Bifidobacteria and Lactobacilli, which have prebiotic properties that lower intestinal pH and inhibit the formation of pathogens [10].



**Figure 2** Effects of feeding patterns during the first 6 months on weight development of infants ages 0–12 months [4].

Most proteins are synthesized by the mammary gland, with a few possible exceptions, such as serum albumin (which appears from the maternal circulation).

### 1.2.3 Digestive Functions

**Bile Salt-Stimulated Lipase.** Bile salt-stimulated lipase in human milk could assist in fat digestion for newborns, particularly preterm infants with limited lipase activity and poor absorption. Studies have demonstrated that boiling breast milk, which deactivates this enzyme, reduces fat absorption in preterm newborns [11]. Because of its broad substrate specificity, this enzyme may aid in lipid

digestion in full-term newborns by breaking down mono-, di-, and triacylglycerols, cholesterol esters, diacylphosphatidylglycerols, and both micellar and water-soluble substrates.

Amylase. Breast milk includes considerable levels of  $\alpha$ -amylase, which remains active in low pH environments and resists pepsin destruction. Although human milk lacks amylase substrates, it is thought that breast milk amylase may compensate for low levels of salivary and pancreatic amylase in neonates, as well as aid in the digestion of complex carbohydrates when solid foods are introduced alongside breastfeeding [11]. However, it is unclear if this has a significant impact on carbohydrate digestion in infants who are breastfed and given complementary foods.

$\alpha$ 1-Antitrypsin. The protease inhibitors  $\alpha$ 1-antitrypsin and antichymotrypsin are present in human milk at levels that could have physiological significance. These inhibitors may reduce the activity of pancreatic enzymes in breastfed infants, acting as natural "brakes." Studies have shown that some milk proteins, including  $\alpha$ 1-antitrypsin, may partially resist digestion and are found in the stool of breastfed infants. In vitro research indicates that adding  $\alpha$ 1-antitrypsin to human milk increases the amount of lactoferrin that resists proteolytic breakdown.

#### 1.2.4 Insulin-Like Growth Factor-Binding Proteins

Insulin-like growth factors (IGFs) I and II are found in human milk and are predominantly connected with IGF-binding proteins. These binding proteins may shield IGF-I and IGF-II from digestion, prolong their half-life, and modulate their interaction with intestinal receptors. Once IGF-I and IGF-II bind to enterocytes, they can act locally in the intestines and potentially spread throughout the body.

#### 1.2.5 Antimicrobial Activity of Human Milk Proteins

Lactoferrin. Lactoferrin has been attributed with multiple antimicrobial properties, one of which may result from the formation of lactoferricin, a potent bactericidal peptide produced during lactoferrin digestion. Recent research indicates that lactoferricin inhibits the attachment of enteropathogenic *E. coli* (EPEC) to intestinal cells, [5] likely due to the serine protease activity of lactoferrin. By breaking down the protein structures necessary for EPEC's attachment and invasion, lactoferrin helps prevent infection. Thus, lactoferrin's various activities play a significant role in protecting against bacterial infections.

Lysozyme. Lysozyme is a key component of the whey fraction in human milk and is an enzyme that can break down the cell walls of gram-positive bacteria by hydrolyzing  $\beta$ -1,4 linkages in N-acetylmuramic acid and 2-acetylamino-2-deoxy-d-glucose residues. Recent research has shown that adding recombinant human lysozyme to chicken feed can act as a natural antibiotic, suggesting it might be an alternative to conventional antibiotic drugs.

$\kappa$ -Casein.  $\kappa$ -Casein, a minor subunit of casein in human milk, is a glycoprotein with charged sialic acid residues. Its highly glycosylated structure has been found to inhibit the adhesion of *Helicobacter pylori* to the human gastric lining [10]. As *H. pylori* infections are increasingly common in younger age groups, breastfeeding may offer protection [12]. The carbohydrate component of  $\kappa$ -casein is believed to be responsible for this protective effect, as similar glycosylated

proteins like sIgA show the same activity, which is lost when they are deglycosylated.  $\kappa$ -Casein acts as a receptor analogue, preventing bacteria from attaching to the mucosal lining.

### 1.2.6 Side Effects of Milk Consumption

Although studies have suggested that milk and milk-product consumption may influence growth during childhood and puberty, results are inconsistent.

**Obesity.** The global rise in childhood obesity is a significant concern. Studies show that at least 60% of children who are overweight before puberty will remain overweight into early adulthood, increasing their risk of cardiovascular disease (CVD) and type 2 diabetes. Interestingly, dairy consumption has been found to have an inverse, long-term relationship with childhood obesity and overweight. However, concerns have been raised regarding the early protein hypothesis. Evidence consistently shows that infants fed formula with higher protein content than human milk during their first year tend to have greater abdominal fat by ages 2 to 6, likely due to elevated levels of IGF-1 and insulin. Insulin, in particular, promotes fat deposition and is a key factor in the early development of insulin resistance.

**Lactose Intolerance.** Though it's much less common in infants than in older children and adults. Lactose intolerance occurs when the infant lacks sufficient amounts of lactase, the enzyme needed to digest lactose, the sugar found in milk. Symptoms of lactose intolerance can include bloating, diarrhoea, gas, and stomach cramps. However, this condition is more likely to develop as the child ages.

**Milk Anaemia.** Excessive drinking of cow's milk in infancy can lead to this condition, in which milk replaces other iron-rich items in the diet, resulting in a lower iron intake. Milk is also poor in key fatty acids and vitamins, such as vitamin E, which are necessary for newborn brain development and overall growth. For these reasons, physicians frequently recommend breast milk or iron-fortified formula as the primary dietary sources for infants in their first year of life [6].

**Cow's Milk Protein Allergy (CMPA).** This impacts only a small minority of babies. CMPA develops when an infant's immune system reacts unfavourably to the proteins in cow's milk, causing symptoms such as vomiting, diarrhoea, skin rashes, wheezing, and, in severe cases, anaphylaxis. Infants with this syndrome may also exhibit irritation and pain after eating, resulting in feeding difficulties, weight loss, or failure to thrive [13, 14].

## 1.3 Significance of Milk in Adults

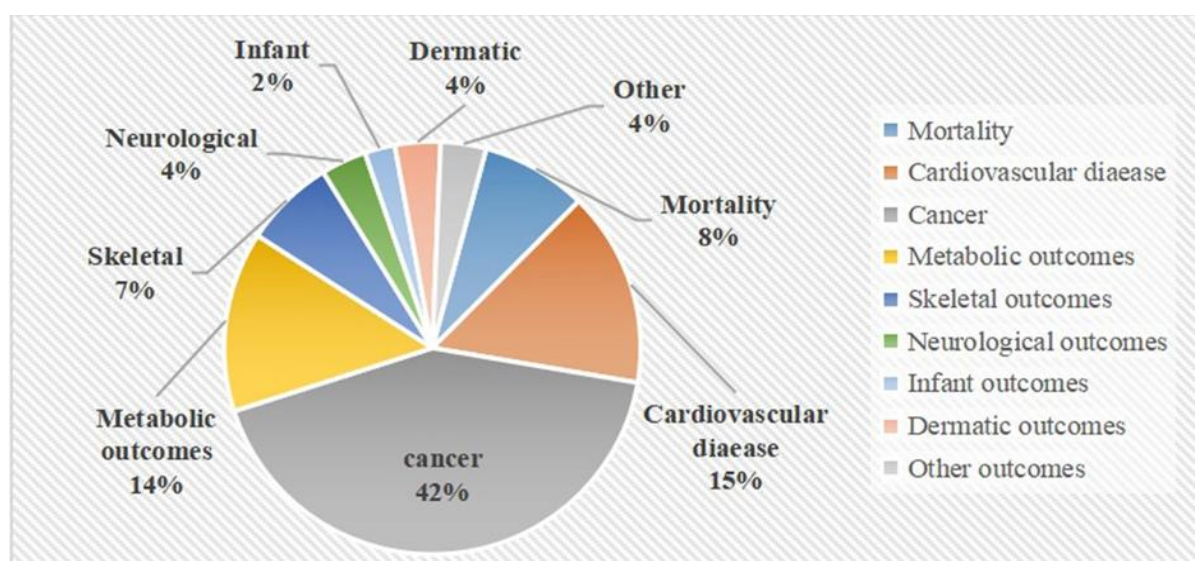
Ageing is explained by several hypotheses at the molecular, biological, systemic, and cellular levels. The human body experiences various physical, physiological, and cognitive changes as we age. For good aging, a proper diet is a crucial influence. Incorrect food habits among the aged result in the advancement of several communicable yet chronic diseases, such as type II diabetes, atherosclerosis, coronary heart disease, and malnutrition. This reduces quality of life and causes declines in cognitive and physical performance [8]. Numerous physical changes brought about by aging have a detrimental overall impact on the health and way of life of the elderly.



The main risk factors for some chronic diseases and declining age-related health are these growing dietary deficits. Milk plays a significant role in maintaining dietary balance.

Dairy products and milk are excellent providers of high-quality protein. Because of its strong satiating effect, which helps to avoid overconsumption of energy and consequently lowers body fat reserves, protein is vital during weight loss and subsequent weight maintenance. Dairy protein also contributes to the upkeep of metabolically active muscle mass after weight reduction because it is a rich source of necessary amino acids for muscle protein synthesis.

Figure 3 illustrates the relative proportions of various health outcomes examined in studies on milk consumption. The outcomes are categorized into ten groups: cancer (42%), cardiovascular disease (15%), metabolic outcomes (14%), mortality (8%), skeletal outcomes (7%), dermatologic (4%), neurological (4%), infant outcomes (2%), and other outcomes (4%). The chart highlights that cancer-related outcomes represent the most significant focus area in the literature, followed by cardiovascular and metabolic health. This distribution underscores the diverse range of health concerns potentially linked to milk intake and emphasizes the need for a balanced and comprehensive evaluation in dietary recommendations.



**Figure 3** Distribution of Health Outcomes Associated with Milk Consumption [5].

### 1.3.1 Role of Milk in Obesity and Diabetes in the Elderly

Despite decades of significant research on the health benefits of dairy products, there is still debate and uncertainty surrounding the relationship between dairy consumption and the risk of type 2 diabetes (T2D) [15]. Reviews that have been published indicate that while milk and other dairy products do not directly contribute to childhood obesity, [8] they do have a significant impact on a child's diet. It's odd, then, that public health recommendations regarding children's dairy product consumption are frequently viewed as ambiguous [16].

Evaluating the impact of milk and dairy products on body weight control is pertinent because the obesity epidemic is primarily to blame for the ongoing rise in the incidence of type 2 diabetes. The contemporary obesity epidemic is primarily due to childhood overweight and obesity, which often follows a child into adulthood. Consequently, it's critical to avoid childhood obesity as early as

possible. A meta-analysis revealed no correlation between dairy intake and obesity in preschool- and school-aged children. During adolescence, there was a slight protective effect, nevertheless.

A diet rich in milk and dairy products improves adult body composition and lowers the likelihood of juvenile obesity [17]. This probably helps to reduce the chance of getting type 2 diabetes. Furthermore, eating dairy products during calorie restriction helps people lose weight; nevertheless, it's unclear how dairy consumption affects energy balance. Lastly, there is mounting data that suggests a lower risk of type 2 diabetes, particularly about fermented dairy products like yoghurt and cheese [15].

### 1.3.2 Role of Milk in Hypertension and Cardiovascular Disease in the Elderly

There is an inverse relationship between blood pressure and dietary calcium, according to epidemiological research [18]. Despite being inconclusive, experimental data have indicated that calcium supplementation is a valuable strategy for managing mild to moderate hypertension. Although excessive calcium intake has been connected to several detrimental health effects in adults, dietary calcium is also believed to enhance lipid metabolism [19].

There is still some ambiguity surrounding the relationship between adult cardiovascular disease (CVD) and milk consumption; depending on several variables, the data may indicate neutral and positive relationships. The positive effects of calcium, dairy fat, and proteins on hunger, fat metabolism and excretion, and the metabolic activity of gut microbiota are among the hypothesized processes that underlie the relationship between dairy nutrients and obesity and cardiometabolic disease, albeit these mechanisms have not been fully clarified. Numerous questions still need to be answered, such as the impacts of various dairy products and their varying fat contents [15].

According to recent research, moderate milk drinking (200-250 mL daily) does not appear to raise the risk of cardiovascular disease substantially. Due to the presence of bacteria and calcium in fermented dairy products like yogurt and some cheeses, some studies even suggest that dairy products may help prevent heart disease, stroke, and high blood pressure. Both inflammation and cholesterol are essential for cardiovascular health, and these components may help lower them.

## 1.4 Lactogenesis

Lactogenesis is the process of milk secretion established in the mammary glands and occurs primarily in two stages: Lactogenesis I, followed by the lactogenic hormones trigger; whereas Lactogenesis II only happens after parturition (formation or delivery). Lactogenesis, commences during the 24th week of pregnancy and remains until approximately the first two days after birth. This stage is defined by transforming mammary epithelial cells into milk-secreting cells under hormonal influence, mainly through increments in progesterone, estrogen, and prolactin levels [7]. Even though the mammary glands start functioning and may even secrete colostrum - a thick, yellowish substance abundant in antibodies, as well as nutrients — high progesterone levels prevent milk from being fully secreted. Lactogenesis II is said to occur from 2-4 days postpartum and represents the onset of copious milk production. The decrease in progesterone occurs following the delivery of the placenta and signals this stage into being, while prolactin levels continue to remain high, which allows for lactation. The milk volume increases, and the composition of the produced milk also starts to adjust, changing from colostrum into mature milk. This stage is susceptible to the suckling of infants and causes the release of prolactin, and oxytocin which in turn helps increase not

only the production but ejection of milk as well [7]. Lactogenesis stage 2 is suspected to be “delayed” if copious milk production has not begun by 72 h postpartum. Milk is supplied and demanded in the production of milk. This involves the need for oxytocin release to empty the mammary gland. Oxytocin from the posterior pituitary acts on myo-epithelial cell receptors to initiate systemic intramammary cross-massage and is produced by infant suckling which stimulates oxytocin release. This causes cells to contract and thereby discharge milk from the breast. Once lactation is established, milk synthesis is controlled by a polypeptide “feedback inhibitor of lactation”. When breastmilk is not sufficiently removed by infant sucking or removal, this initiates the accumulation of feedback inhibitor of lactation resulting in decreased milk production and ultimately mammary involution [20]. Apoptosis of milk-synthesizing epithelial cells appears to cause the decline in milk volume with cessation of breastfeeding [12]. The mammary gland during this process undergoes an intense tissue remodelling and reversion of a pregnant to non-pregnant state (termed mammary involution).

In summary, lactogenic activity is a multifaceted process that occurs predominantly under the regulation of hormones and has been crucial for feeding neonatal mammals with the nutrients necessary for life-support sustenance [21].

## **2. Materials and Methods**

### **2.1 Study Design**

The systematic review by Soedamah-Muthu et al. [5] may have limited their meta-analysis in reflecting the complete range of evidence on the health effects of milk, particularly if milk intake has a different influence compared to other dairy items. For example, cheese and yogurt possess unique nutrient profiles and preparation techniques relative to milk, potentially affecting health results in various ways. By PRISMA criteria for meta-analysis of observational studies, a systematic search and quantitative analysis were organized, carried out, and published [22]. The PRISMA statement aims to assist authors in improving how systematic reviews and meta-analyses are reported [23]. Failure to isolate milk-specific data may lead to Soedamah-Muthu et al.'s findings not accurately representing milk's distinct contributions to health outcomes [5]. The 1984 study was part of the analysis because it offered particular information on milk consumption that had not been examined in Soedamah-Muthu et al.'s review. Incorporating it expands the analysis by filling a possible gap: research previously omitted due to a lack of milk-specific information [5].

### **2.2 Search Strategy**

In the meta-analysis conducted by Soedamah-Muthu et al., rigorous inclusion criteria were set to guarantee the dependability and precision of the results related to milk intake and health effects. The inclusion of studies depended on their prospective design, an essential factor that reduces recall bias and offers more robust evidence of temporal links between milk consumption and health outcomes [24, 25]. Prospective cohort studies efficiently investigate dietary habits and their long-term health impacts, making them perfect for this analysis [5].

## **2.3 Extraction of Data**

The primary outcomes chosen for the analysis included all-cause mortality, coronary heart disease (CHD) (both fatal and non-fatal), and stroke (both fatal and non-fatal). These results were selected because of their significant effects on public health and the possibility that milk consumption could affect their risk profiles [24]. The thorough data extraction method utilized in the research by Soedamah-Muthu et al. demonstrates the elevated methodological standards required for performing a strong meta-analysis. Through the meticulous selection of pertinent outcomes and consideration of confounders, the research offers important insights into the intricate link between milk intake and significant health outcomes, establishing a foundation for future investigations in this field [5].

## **2.4 Data Analysis**

Using standard conversions from the Food Standards Agency, milk intake was transformed from servings or other units into milliliters per day. An average of 200 milliliters was equivalent to one dish or glass of milk. A first linear model was fitted for dose-response analysis within each trial to quantify the relative risk for each unit increase in drink.

The significance level for all two-sided statistical tests was set at 0.05 [2]. Studies adjusted for age, body mass index (BMI), total energy consumption, and physical activity underwent different analyses to examine the origins of heterogeneity.

## **3. Results**

Table 1 illustrates the meta-analysis that examines the relationship between consuming 200 mL of milk daily and these outcomes, considering important confounders like age, BMI, total energy intake (TEI), and physical activity (PA). This study seeks to enhance the understanding of milk's contribution to overall and cardiovascular health by analyzing data from various cohorts. The emphasis on physical activity as a central aspect probably demonstrates an attempt to consider confounding factors that might affect the link between milk intake and health results. Exercise is a well-recognized element influencing heart health, stroke likelihood, and overall mortality. Not accounting for this variable could either overstate or understate the actual impact of milk consumption.

**Table 1** Results of meta-analyses and sensitivity analyses for 200 mL/d milk and all-cause mortality, fatal and non-fatal coronary heart disease and stroke [21].

| Analyses                                   | No. Cohorts | SRR  | 95% CI |      | I <sup>2</sup> (%) | 95% CI |    | Begg test | Egger test | Macaskill test |
|--------------------------------------------|-------------|------|--------|------|--------------------|--------|----|-----------|------------|----------------|
| All-cause mortality                        |             |      |        |      |                    |        |    |           |            |                |
| All cohorts                                | 11          | 1.01 | 0.96   | 1.06 | 94                 | 92     | 96 | 0.76      | 0.64       | <0.01          |
| Men only                                   | 4           | 1.00 | 0.92   | 1.09 | 81                 | 50     | 93 | 1.00      | 0.24       | 0.38           |
| Adjusted for age, BMI, TEI, and PA         | 6           | 1.04 | 0.95   | 1.13 | 96                 | 93     | 97 | 0.85      | 0.67       | <0.01          |
| All but Michaëlsson et al.                 | 9           | 0.99 | 0.95   | 1.03 | 63                 | 24     | 82 | 0.83      | 0.15       | 0.24           |
| Fatal and NON-FATAL coronary heart disease |             |      |        |      |                    |        |    |           |            |                |
| All cohorts                                | 9           | 1.01 | 0.98   | 1.05 | 16                 | 0      | 58 | 0.68      | 0.05       | 0.58           |
| Men only                                   | 4           | 0.99 | 0.91   | 1.08 | 25                 | 0      | 88 | 0.17      | 0.61       | 0.50           |
| Adjusted for age, BMI, TEI, and PA         | 4           | 1.03 | 0.97   | 1.08 | 0                  | 0      | 65 | 0.50      | 0.58       | 0.98           |
| All but Hu et al.                          | 8           | 1.01 | 0.96   | 1.05 | 18                 | 0      | 61 | 0.46      | 0.11       | 0.54           |
| Fatal and NON-FATAL stroke                 |             |      |        |      |                    |        |    |           |            |                |
| All cohorts                                | 10          | 0.91 | 0.82   | 1.02 | 92                 | 87     | 95 | 0.53      | 0.05       | <0.01          |
| Men only                                   | 5           | 0.96 | 0.86   | 1.09 | 60                 | 0      | 85 | 0.62      | 0.24       | 0.03           |
| All but Abbott et al.                      | 9           | 0.92 | 0.82   | 1.04 | 92                 | 88     | 95 | 0.60      | 0.07       | <0.01          |

SRR = summary relative risk; CI = confidence interval; BMI = Body Mass Index; TEI = total energy intake; PA = physical activity.

People who exercise regularly may have different eating patterns, such as milk consumption, in contrast to those who are inactive. Engaging in physical activity may independently lower the risk of CVD and death, possibly obscuring the relationships between milk consumption and these results [21].

One paper from 1984, which was left out of the Soedamah-Muthu et al. meta-analysis, was added. Five studies chosen by Soedamah-Muthu et al. were not included in our analysis because there was a lack of data on milk intake specifically or the data was about dairy products rather than milk [5]. The cohort studies include wide range of ages, BMI, TEI, PA for all-cause mortality, coronary heart disease, and fatal and non-fatal stroke [5].

### **3.1 Total Mortality**

#### **3.1.1 Overall Analysis**

A summary relative risk (SRR) of 1.01 (95% CI: 0.96-1.06) indicated that no statistically significant link exists between physical activity (PA) and mortality from all causes. This study suggests that engaging in physical activity might not significantly reduce the total risk of mortality.

#### **3.1.2 Male-Only Subgroup**

A similar non-significant correlation was observed with an SRR of 1.00 (95% CI: 0.92-1.09) when the analysis focused exclusively on male participants. The finding that PA might not significantly affect men's all-cause mortality is additionally backed by this alignment with the overall data.

#### **3.1.3 Modified Analysis**

The SRR for the association between PA and overall mortality rose slightly to 1.04 (95% CI: 0.95-1.13) following adjustments for possible confounding factors such as age, body mass index (BMI), total energy intake (TEI), and physical activity level. This modified correlation, however, also remained statistically non-significant, suggesting that the general connection between PA and mortality risk is not notably altered by these confounding variables.

### **3.2 Lethal and Non-Lethal Coronary Heart Disease (CHD)**

#### **3.2.1 General Assessment**

The relationship between coronary heart disease (CHD) and physical activity was not significantly correlated. With a calculated SRR of 1.01 (95% CI: 0.98-1.05), engaging in physical exercise may not notably reduce the risk of CHD.

#### **3.2.2 Male-Only Group**

Consistent with the overall results, the research exclusively focused on male participants and revealed no significant relationship. The subgroup's SRR of 0.99 (95% CI: 0.91-1.08) indicated that physical activity might not significantly contribute to the risk of coronary heart disease in men.

### **3.3 Lethal and Non-Lethal Stroke**

#### **3.3.1 General Research**

The study discovered a notable negative relationship between physical activity and stroke risk, unlike all-cause mortality and coronary heart disease. The SRR was 0.91 (95% CI: 0.82-1.02), indicating that PA might protect against strokes. The trend suggests that consistent exercise might lower the occurrence of both fatal and non-fatal strokes, despite this finding not reaching traditional statistical significance.

#### **3.3.2 Men-Only Subgroup**

An SRR of 0.96 (95% CI: 0.86-1.09) indicated a similar negative association when focusing on male subjects. This suggests that men who work out might experience a reduced risk of stroke, despite the lack of statistical significance in the correlation.

#### **3.3.3 Sensitivity Analysis**

One study was omitted to perform a sensitivity analysis and assess the robustness of the results. The ultimate SRR, recorded at 0.92 (95% CI: 0.82-1.04), did not markedly differ from the final result. This consistency indicates that PA might indeed possess a preventive influence on stroke and demonstrates that the noted inverse relationship is relatively enduring. Given these findings, it remains uncertain how physical activity influences CHD and overall mortality [21].

### **3.4 Heterogeneity and Publication Bias**

High heterogeneity was observed in all-cause mortality and stroke analyses ( $I^2 > 80\%$ ), whereas CHD analyses showed low heterogeneity ( $I^2 < 20\%$ ). Publication bias tests, including Begg's and Egger's, were largely non-significant across all outcomes. However, the Macaskill test suggested potential small-study effects for all-cause mortality and stroke ( $p < 0.01$ ), warranting cautious interpretation of those findings.

### **3.5 Subgroup Analyses and Sensitivity Checks**

#### **3.5.1 Gender Differences**

Risk estimates did not vary substantially between all cohorts and male-only subgroups.

#### **3.5.2 Adjustment for Confounders**

Adjusting for age, BMI, TEI, and PA resulted in modest changes to the SRRs but did not shift the overall interpretation of null associations.

#### **3.5.3 Sensitivity Analyses**

Removal of potentially influential studies (Michaëlsson et al.) reduced heterogeneity and produced only minor changes in effect estimates [21].

## 4. Discussion

The findings obtained through this meta-analysis are enlightening regarding the relationship of milk consumption to meaningful health outcomes, including all-cause mortality, coronary heart disease (CHD), and stroke. Overall, the findings indicate no significant association between the daily intake of 200 mL of milk and all-cause mortality or CHD risks. Still there was a possible protective trend in the case of stroke, though not statistically significant. These findings are characteristic of the complex impact of milk on human health and underscore the significance of cautious interpretations in creating dietary guidelines [25]. Our meta-analysis of prospective observational cohort studies revealed no hint of a connection between milk consumption and all-cause mortality, fatal or non-fatal coronary heart diseases, and non-fatal or fatal stroke [24, 25]. But be mindful of the fact that, by definition, such meta-analyses are subject to the limitations of observed data, in particular to the possibility of having confounding variables and study biases. Such limitations include differences between studies in food measurement, inconsistencies in self-reporting, and heterogeneity in adjustment for lifestyle variables, e.g., physical activity, smoking, and overall food quality. Publication bias can also exist, which may cause underestimation of trials showing higher evidence of stroke or risk of death with higher consumption of milk. This selective publication of results biases the pooled estimates and leads to less awareness of potential hazards. The results of the Swedish cohort and the meta-analysis conducted by Soedamah-Muthu et al. were contradictory [5]. They can be taken to reflect the wide range of results reported in prospective studies of milk consumption and its association with coronary heart disease, stroke, and all-cause mortality [5].

This meta-analysis found no meaningful association between milk consumption and fatal or non-fatal coronary heart disease, stroke, or all-cause mortality. This finding contradicts the long-standing problems with milk's saturated fat impacting cardiovascular risk. Milk is also a source of healthy nutrients like potassium, which helps to control blood pressure, and bioactive peptides, which have protective functions on the heart [24, 25]. These nutrients can counteract the potential risks of its fat.

For women, the nutritional importance of milk is often emphasized because it guards against osteoporotic fractures, which are two to three times more frequent in women than in men. Calcium and vitamin D, which are high in milk, play a key role in the integrity of the bones, and the growing awareness of osteoporosis can lead to greater consumption of milk as a preventive factor against fractures [26]. However, this beneficial practice among women may be misleading because people who drink more milk may also have other positive lifestyle characteristics—such as improved diet, increased physical activity, and regular health checkups—that are independently associated with reduced risk of adverse health effects. This makes it challenging to isolate the impact of milk alone. Although women drink milk primarily for bone health, its role in cardiac health is more complex. Cardiovascular disease (CVD) is the leading cause of death in women globally, but its risk factors as well as symptoms may differ substantially compared to men. For instance, women develop CVD at an older age, and their symptoms are usually unusual, making it harder to diagnose and treat them. During pregnancy and lactation, milk consumption plays a key role in meeting the increased nutritional needs of the mother and her growing fetus. Adequate calcium and vitamin D consumption is critical in fetal bone formation and the mother's bone health. Further, the protein and micronutrients of milk are involved in the general health of mothers and infant development [26].



Some of the limitations in the literature also make interpreting these findings more difficult. These include heterogeneity of study population, study design, and type of milk (e.g., whole, skim, or fortified). The nutritional composition of milk is quite different by fat content and fortification, which is not always controlled in studies. Whole milk contains more saturated fat, and skim milk contains the exact quantities of protein and minerals but less fat. Differences like these are rarely the same across studies, and therefore comparisons are not straightforward and result in conflicting conclusions. Furthermore, residual confounding remains a genuine issue. Individuals who drink milk frequently could also engage in healthy lifestyle habits, such as following a nutritious diet, regular exercise, or reduced alcohol consumption. Such lifestyle variables might directly affect cardiovascular disease and death, thereby skewing the relationships observed. Such variables are complex to adjust for, primarily based on self-report, which is frequently filled with recall bias and inaccuracy.

In conclusion, while this meta-analysis is very informative, it is essential to appreciate these interpretation limitations. More high-quality randomized controlled trials and prospective long-term studies with strict methodological controls need to be done to determine more conclusively the role of milk in cardiovascular and overall health outcomes.

#### **4.1 Therapeutic Potential of Dairy By-Products**

Beyond their conventional nutritional worth, recent research has shown that dairy by-products including whey and colostrum have promising health benefits. Ceniti et al. [27] found that ovine colostrum and milk whey have potent antiproliferative effects on chronic myeloid leukemia (K562) cells, triggering apoptosis and changing cell cycle progression. This implies possible uses in cancer therapy and emphasizes the bioactivity of dairy products.

Further study has revealed many bioactive substances in dairy by-products with significant health-promoting properties:

##### **4.1.1 Immunoregulatory and Antibacterial Compounds**

Bacteriocins, like pediocin and nisin, are produced when lactic acid bacteria (LAB) ferment whey. These compounds have potent antibacterial activity against pathogens like *Listeria monocytogenes*. These chemicals also have immunomodulatory properties, which boost the body's defense mechanisms [22].

##### **4.1.2 Cardiovascular and Metabolic Health**

Lactoferricin and other bioactive peptides made from whey proteins have antihypertensive properties through preventing the activity of the angiotensin-converting enzyme (ACE). These peptides also have antibacterial, antifungal, antiviral, and anti-inflammatory properties, contributing to cardiovascular and metabolic health [24, 25].

##### **4.1.3 Skin Health and Wound Healing**

Whey proteins have been shown to improve skin health by increasing collagen synthesis, blocking enzymes such as elastase and tyrosinase, and strengthening the skin barrier [22]. Furthermore,

ovine milk whey has been demonstrated to speed wound healing in human gingival fibroblasts, implying potential in dermatological applications.

## **5. Emerging Perspectives and Future Directions**

Recent advances in nutritional science have opened up new possibilities for understanding milk's varied impact across the life cycle. One intriguing topic is the relationship between milk consumption and the gut-brain axis, specifically fermented dairy products, which may influence mental health by modifying gut microbiota and neurotransmitter pathways [28]. Furthermore, identifying human milk oligosaccharides (HMOs) as neurodevelopmental modulators via microbiota maturation emphasizes breastfeeding's cognitive relevance beyond its traditional nutritional activities [29]. Milk-derived extracellular vesicles, such as exosomes, are being investigated molecularly for their epigenetic regulatory potential, which has implications for immunological development and chronic disease susceptibility [30]. These insights support the notion that milk serves not only as sustenance but also as a dynamic bioactive medium.

Concurrently, the emergence of plant-based milk alternatives has sparked interest in fortification measures to assure nutritional balance and sustainability, raising ethical concerns about food fairness and environmental responsibility. Furthermore, precision nutrition techniques currently argue for tailored dietary guidelines that consider variations in metabolic response to dairy components such as A2 casein and dairy peptides [31]. Together, these developing elements underline the changing complexity of milk's function in health and the significance of incorporating molecular, ecological, and personalized frameworks into future research and dietary recommendations [27].

## **6. Conclusion**

Milk is a vital part of human nutrition, offering a rich supply of essential nutrients that support growth, development, and overall health throughout different stages of life. The proteins, vitamins (like A, D, and B12), and minerals (notably calcium and phosphorus) it contains are crucial for many physiological functions. The relationship between milk intake and heart health is intricate and diverse. While traditional dietary recommendations have raised concerns about the contribution of milk's saturated fat to cardiovascular disease (CVD), recent findings suggest a more intricate scenario. Our meta-analysis indicated that moderate milk intake (approximately 200 mL daily) does not considerably increase the risk of cardiovascular disease or overall mortality. Conversely, certain studies suggest that milk could possess protective effects against strokes. This may be associated with bioactive peptides, potassium, and various minerals that aid in regulating blood pressure and lowering inflammation. Considering the inconsistent and diverse results of observational studies, it is clear that a universal method for dietary recommendations is insufficient. Personalized nutrition, considering individual factors like age, health condition, genetic factors, and lifestyle choices, is essential for enhancing health results. Furthermore, rising information on the medicinal potential of dairy byproducts necessitates further investigation into their bioactive components, mechanisms of action, and clinical applications. Incorporating omics technologies, microbiome profiling, and precision nutrition frameworks could provide more insight into milk's personalized health benefits. Bridging these knowledge gaps is critical for converting scientific discoveries into balanced, evidence-based consumption guidelines that improve population-wide and individual health

outcomes. The findings indicate that, while milk remains an essential dietary component, its benefits and hazards are influenced by age, dosage, metabolic setting, and the kind of milk consumed. These findings promote the revision of current dietary guidelines to account for individual variability and life-stage-specific demands, rather than promoting a one-size-fits-all approach.

## **Author Contributions**

Upama Majumder contributed to the conceptualization and drafting of the manuscript, including literature synthesis, analysis, and interpretation of findings. She also participated in writing multiple core components of the manuscript and was actively involved in refining the narrative. Samayeta Pramanik contributed significantly to writing, interpretation, and critical analysis of the content. She was also responsible for formulating conclusions and developing discussions based on the study findings. Additionally, she participated in co-authoring the introductory framework and final revisions. Mobasshara Uzma contributed by conducting literature review, assisting in data analysis, and co-developing key methodological content. Kavya P R contributed to data extraction, research methodology, and literature consolidation. Debasish Kar supervised the project, provided technical oversight and intellectual input throughout the drafting process, and critically reviewed the manuscript for scientific accuracy and coherence.

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## **Competing Interests**

The authors have declared that no competing interests exist.

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