

Dairy Long Term Intake Guideline for the Prevention of Cardiovascular Disease: A Population Based Cohort Study from Eastern Mediterranean Regional (EMR)

Rahelah Karimi¹, Marjan Mansourian^{1*}, Shaghayegh Haghjooye Javanmard², Raziieh Hassannejad³, Hamidreza Roohafza⁴, Noushin Mohammadifard⁴, Masoumeh Sadeghi⁴, Nizal Sarrafzadegan⁴

¹Department of Epidemiology and Biostatistics, Isfahan University of Medical Sciences, Isfahan, Iran; ²Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran; ³Department of Biostatistics, Isfahan University of Medical Sciences, Isfahan, Iran; ⁴Department of Cardiology, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Despite the common belief that recommended whole fat dairy products, a reasonable intake of dairy fat may also lower risk of cardiovascular disease. To investigate this relationship, dairy comprised for 1387 individuals were recorded and the risk of cardiovascular events (CVD, IHD and stroke) were assessed using cox regression model. The results showed that total dairy more than five servings per week reduced risk of CVD by 75%, and serving 3-5 was associated with lower risk of stroke (35%). About high-fat dairy, intake of 3-5 servings per week, reduced risk of stroke by 67%, and lower risk of CVD was observed in consumption of <3 servings of high-fat dairy by 80%. Three-five serving of low fat dairy, only reduced the risk of CVD (64%), similarly for intake of <3 compared with zero intake. As a result, dairy consumption was associated with lower risk of major cardiovascular disease events especially CVD and stroke.

Keywords: Dairy products; Stroke; Cardiovascular disease; Whole fat

INTRODUCTION

Cardiovascular Diseases (CVD), includes Coronary Heart Disease (CHD) and the diseases related to cerebral vessels are one of the top 10 causes of mortality worldwide, accounting for approximately 30% of all deaths Cardiovascular Diseases (CVDs). According to the World Health Organization (WHO) statistics, an estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. CVD is the most important cause of disabilities and death in Iran. Coronary artery disease causes mortality, morbidity and disability in the Iranian population and it almost accounts for 50% of all deaths per year. These diseases impose huge costs on health systems in countries, however, it is preventable. It seems that changes in lifestyle such as consumption of unhealthy or poor diet, lack of physical activity, an increase in the prevalence of obesity and smoking, have led to a progressive increase in the prevalence of coronary heart disease in developed countries. In fact, diet and lifestyle are important factors for the prevention of CVD, so the search effort have concentrated on life-style adjustment milk and dairy products are important nutrients constituent of a healthy diet as they are a major source of energy, protein, and provide

essential vitamins that are important for growth, development and tissue maintenance. Also, dairy products are major source of cholesterol raising Saturated Fatty Acids (SFAs) which can adversely affect blood lipids and increase cardiovascular disease, as it may lead to increased Low-Density Lipoprotein cholesterol (LDL) levels [1]. The consumption of dairy, particularly low fat dairy is recommended by cardiovascular health in most dietary guidelines, is that low fat dairy foods are a major source of high plasma LDL cholesterol and are a key risk factor for Coronary Artery Disease (CAD), however, dairy fat products also contain potentially beneficial compounds such as specific amino acids, phospholipids, natural trans fats, vitamin K1 and K2, calcium, and can contain probiotics, which might affects on health outcomes. In fact, some strong evidence suggests the consumption of dairy foods, including milk, cheese and yogurt, can help to protect cardiovascular health. For example, a meta-analysis of 31 prospective cohort studies published in 2016 by Alexander et al., showed that calcium from dairy consumption, including whole-fat dairy and full-fat dairy were associated with a 31% and 9% lower risk of stroke, respectively. Researches showed that consumption of cheese was associated with an 18%

Correspondence to: Marjan Mansourian, Department of Epidemiology and Biostatistics, Isfahan University of Medical Sciences, Isfahan, Iran, Tel: 989139584937; E-mail: jmansourian@gmail.com

Received: 14-February-2022, Manuscript No. JNFS-22-15850; **Editor assigned:** 17-February-2022, PreQC No. JNFS-22-15850 (PQ); **Reviewed:** 03-March-2022, QC No. JNFS-22-15850; **Revised:** 30-November-2022, QI No. JNFS-22-15850; Manuscript No. JNFS-22-15850 (R); **Published:** 28-December-2022, DOI: 10.35248/2155-9600.22.12.1000893

Citation: Karimi R, Mansourian M, Javanmard SH, Hassannejad R, Roohafza H, Mohammadifard N, et al. (2022) Dairy Long Term Intake Guideline for the Prevention of Cardiovascular Disease: A Population-Based Cohort Study from Eastern Mediterranean Regional (EMR). J Nutr Food Sci. 12: 893.

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and 13% reduced risk of coronary heart disease and stroke, respectively. The prospective cohort study provides a unique opportunity to study the associations of dairy intake and types of dairy products with cardiovascular disease. Overall, studies on the relationship between dairy consumption and cardiovascular disease were short term cohort and studies that have examined long term consumption of dairy are scarce. Therefore, in this study, for the first time in the region, our we assess the associations between long-term consumption of dairy products on major cardiovascular disease [2].

MATERIALS AND METHODS

Study design and participants

Isfahan Cohort Study (ICS) included 6504 individuals aged equal or more than 35 years who had complete information by questionnaires, and recruited from January to September 2001. Participants came from three central areas of Iran and were selected by using multistage random sampling based on age, gender and urban/rural distribution. Data about their diet and some important personal information were collected with standardized questionnaires with informed consent from each participant individually [3]. Data collection process and questionnaires were reported in details before. They were followed to meet major cardiovascular events including heart attack, Ischemic Heart Disease (IHD), stroke and recorded data in the forms. The study consists of three phases, 2001, 2007 and 2013. Validated food frequency questionnaire, anthropometric measurements, blood pressure, fasting serum lipids and blood sugars were evaluated in three phases of the study. Due to lack of dairy information in the first phase, finally a number of 1387 participants in both phases, 2007 and 2013 had complete information and were enrolled in our study. Participants were examined biannually for having any CVD events during the study time. The study approved by the ethics committee of Isfahan Cardiovascular Research Center (ICRC), as a World Health Organization collaborating center [4].

Procedures of dietary assessment

Each participant's habitual food intake was recorded using validated Food Frequency Questionnaires (FFQs), over the three times of study through a face to face interview. Participants were asked how often they had consumed specific foods or drinks, daily, weekly and monthly in the past year, and a list of these food items was given. The reported frequency of consumption for each food item was converted to weekly intake to compute entire frequencies of the food and nutrient intakes. 'Zero' indicates that 'never' or 'rare' food consumption [5].

Dairy comprised milk, cheese, yoghurt and cream that we further grouped them into whole fat dairy (whole fat milk, whole fat yoghurt, whole fat cheese), low fat dairy (low fat milk, low fat yoghurt, low fat cheese) and high fat dairy (high fat milk, high fat yoghurt, high fat cheese, cream), were used for analysis. Butter and cream were not included in the whole fat dairy groups.

Assessment of other covariates

Some important demographic properties, and life style components such as nutrition, smoking, physical activity, depression, family history of CVD, Diabetes Mellitus (DM), lipid profiles such as LDL, HDL, BMI, and blood pressure (HTN) of participants were used as covariates. Demographic properties were extracted from the standardized questionnaires, also for measuring the lipid profiles, blood pressure and anthropometric measurements, fasting blood samples and standard protocols were applied. Whole information about individual status was measured by medical interviews and physical examinations and collected by trained physicians and health professionals [6]. For some variables such as depression we used factor analysis to quantify participant's mental status (low/high) and some were represented as dichotomous variables (Yes/No). For example, DM was defined as if FBS \geq 126 mg/dl or the 2 h post-load plasma glucose \geq 200 mg/dl or the patient was receiving antidiabetic agents. HTN was defined as if blood pressure \geq 140/90 mm Hg or if the patients were receiving antihypertensive drugs. High LDL was defined as if LDL-C \geq 130 mg/dl, and Low HDL was defined as if HDL-C $<$ 40 mg/dl in men or $<$ 50 mg/dl in women. Smoking status was categorized as never or current and physical activity was assessed using the Iranian version of International Physical Activity Questionnaire (IPAQ). Consumption of other foods such as oil, sweets, fast food, fruits and vegetables were also calculated as weekly consumption [7].

Outcomes

The primary outcome was the composite of major cardiovascular events, defined as Cardiovascular Disease event (CVD), stroke or heart failure and Ischemic Heart Disease (IHD) including: Myocardial Infarction (MI), Sudden Cardiac Death (SCD), Unstable Angina (USA). Other outcomes were total mortality and major cardiovascular disease (fatal and nonfatal myocardial infarction, fatal and non-fatal strokes, heart failure, and cardiovascular mortality) [8].

Statistical analysis

Continues variables were expressed as means (SD) and categorical variables as percentages. For the overall analysis, dairy consumption categorized into equal parts and trend analysis was done to examine trend of changing the variables across the quartiles of dairy intake. Categories for milk, yoghurt, cheese, cream and butter consumption were zero, less than two serving per week ($<$ 2 per week), between two and five serving per week (2-5 per week), and more than five serving per week ($>$ 5 per week). The longitudinal relation of dairy intake with CVD, IHD and stroke was evaluated using a multivariate analysis with cox regression model. Estimates of HRs and 95% CIs are presented for categories dairy products in each quartiles and the lowest intake group (first quartile) was used as the reference group [9]. Hazard of cardiovascular event across quartiles of dairy were estimated based on five models including: Crude model and different adjusted strategies models. Analyses were done with R.3.6.0.

RESULTS

Of the total 6504 people, 1387 participants completed the information related to dairy intake, of which 51.4% were women and the average age was 47.4 ± 9.4 . During the follow-up of 7 years, we recorded 520 individuals who had major cardiovascular events (-366 CVD, -108 IHD (MI, SCD, USA), 46 stroke) [10]. Examination in 2007, participants who consumed more dairy (higher quartiles) had lower anxiety disorder

($P=0.001$) and in 2013, participants in the higher quartiles of dairy intake were more likely to be physically active ($P=0.03$). About dietary, participants in higher quartiles of dairy intake, consumed higher some dietary such as fruits, vegetables, liquid oil and sweet across quartiles of dairy intake in both phases ($p<0.001$). Clinical status of participants such as DM, LDL, HDL, blood pressure and family history of CVD were not significantly different in quartiles of dairy intake in 2007 and 2013 (Tables 1 and 2).

Table 1: General characteristics of study participants across quartiles of dairy intake in each study year.

Dairy intake (per weak)	2007						2013					
	1 st (n=346)	2 nd (n=347)	3 rd (n=347)	4 th (n=347)	P trend ^a	Total	1 st (n=346)	2 nd (n=347)	3 rd (n=347)	4 th (n=347)	P trend ^a	Total
Age (year)	47.7 ± 9.4	47.9 ± 8.9	46.7 ± 9.3	47.4 ± 9.4	0.611	47.4 ± 9.2	47.7 ± 9.4	47.9 ± 8.9	46.7 ± 9.3	47.4 ± 9.4	0.284	47.4 ± 9.2
Female	53.7	53.8	47.6	46.9	0.146	51.4	59.8	52.2	47	46.7	<0.001	51.4
BMI (kg/m ²)	27.4 ± 4.4	28.5 ± 4.5	27.8 ± 4.6	28 ± 4.4	0.503	27.8 ± 4.4	28.2 ± 4.5	28.2 ± 4.7	27.7 ± 4.5	28.1 ± 4.9	0.35	28.1 ± 4.6
PA (MET-h/wk)	13.9 ± 8.9	14.1 ± 9.2	15.5 ± 10.1	14.9 ± 8.8	0.605	14.6 ± 9.3	12.1 ± 9.3	12.1 ± 8.6	13.2 ± 9.4	13.6 ± 11.7	0.03	12.8 ± 9.8
Smoker (yes)	19.4	19	21.3	22.8	0.198	20.6	17.7	18.6	17.6	23.6	0.076	19.4
Depression, anxiety (low)	25.4	19.6	18.4	15	0.001	19.6	24.1	14.5	19	19.4	0.326	19.2
DM (yes)	21.4	22.2	21.6	21.3	0.46	21.6	13.9	13.3	14.7	11.2	0.624	13.3
BP (yes)	50.9	50.4	54.5	50.1	0.436	51.5	37.3	44.1	40.6	40.1	0.688	40.5
LDL (high)	48.8	49.6	58.5	50.4	0.109	44.9	50.9	51.9	51.6	53	0.606	51.8
HDL (low)	49.1	43.8	44.1	42.7	0.254	51.8	50	41.5	43.2	45	0.263	44.9
Family history of CVD (yes)	9.5	8.6	23.4	10.1	0.812	9.2	7.8	10.1	9.5	7	0.124	9.2

Note: Quantitative variables were expressed as mean ± sd and qualitative variables were expressed as percent; PA: Physical Activity; BMI: Body Max Index; DM: Diabetes Mellitus; BP: Blood Pressure; LDL: Low-Density Lipoproteins; HDL: High-Density Lipoproteins; CVD: Cardiovascular Disease; aP for trend across dairy quartiles in each study year

Table 2: General nutrition items of study participants across quartiles of dairy intake in each study year.

Dairy intake (per weak)	2007				2013			
	1 st	2 nd	3 rd	4 th	1 st	2 nd	3 rd	4 th

	(n=346)	(n=347)	(n=347)	(n=347)	P trend ^a	Total	(n=346)	(n=347)	(n=347)	(n=347)	P trend ^a	Total
Solid oil	2.7 ± 6.9	2.1 ± 2.9	1.8 ± 2.8	2.2 ± 5.5	0.102	1.42.3	1.29 ± 3.6	1.25 ± 2.8	1.52 ± 2.9	1.16 ± 2.5	0.426	1.3 ± 2.9
Liquid oil	6.1 ± 4.5	5.9 ± 3.2	6.6 ± 3.6	7.04 ± 4.3	0.001	6.4 ± 3.9	4.4 ± 3.9	5.2 ± 3.9	5.6 ± 3.6	5.8 ± 3.7	<0.001	5.3 ± 3.8
Sweets	1.2 ± 2.1	1.3 ± 1.9	1.6 ± 2.5	1.6 ± 2.5	0.023	1.4 ± 2.3	1.5 ± 2.6	1.8 ± 3.3	1.99 ± 3.1	2.4 ± 3.4	<0.001	1.9 ± 3.1
Vegetable	7.3 ± 6.2	8.1 ± 4.5	8.6 ± 4.2	8.9 ± 4.3	<0.001	8.3 ± 4.9	4.8 ± 3.5	5.73 ± 3.9	6.93 ± 6.4	7.3 ± 4.3	<0.001	6.2 ± 4.7
Fruit	6.2 ± 4.3	7.4 ± 4.4	8.5 ± 4.2	9.2 ± 5.7	<0.001	7.8 ± 4.8	6.3 ± 4.5	6.9 ± 4.3	7.8 ± 4.3	8.8 ± 4.7	<0.001	7.4 ± 4.5
Fast food	0.5 ± 1.1	0.65 ± 1.1	0.5 ± 1	0.7 ± 1.3	0.377	0.58 ± 1.2	0.58 ± 1.1	0.52 ± 1.2	0.52 ± 0.96	0.73 ± 1.3	0.053	0.58 ± 1.2
Milk	3.3 ± 2.6	3.9 ± 2.9	3.39 ± 2.8	3.6 ± 2.9	<0.001	3.5 ± 2.8	0.44 ± 0.67	1.2 ± 1.4	1.8 ± 1.9	3.2 ± 3.1	<0.001	1.6 ± 2.2
Cheese	5.9 ± 4.4	6.40 ± 3.1	6.4 ± 1.8	6.6 ± 3.9	<0.001	6.3 ± 2.6	0.30 ± 0.39	0.49 ± 1.3	1.1 ± 2.4	2.4 ± 3.5	<0.001	0.82 ± 2.2
Yoghurt	4.3 ± 2.8	5.42 ± 2.5	5.7 ± 2.2	5.6 ± 2.5	<0.001	5.3 ± 2.6	1.4 ± 1.2	3.7 ± 2.5	4.9 ± 2.8	5 ± 2.9	<0.001	3.8 ± 2.8
Total dairy	9.6 ± 2.6	14.7 ± 0.83	18.3 ± 1.9	23.4 ± 5.5	<0.001	16.5 ± 5.9	2 ± 1.2	5.7 ± 1.2	8.6 ± 1.1	15.6 ± 4.3	<0.001	8 ± 5.6
High-fat dairy ^b	1.1 ± 2.6	1.1 ± 2.3	1.6 ± 3.2	3.6 ± 5.9	<0.001	1.8 ± 3.9	0.8 ± 1.7	1.2 ± 2.2	1.8 ± 2.8	2.9 ± 4.4	<0.001	1.7 ± 3.1
Low-fat dairy ^c	8.9 ± 2.9	13.8 ± 2.3	17.2 ± 3.4	20.2 ± 5.9	<0.001	15.04 ± 5.7	1.9 ± 1.3	5.1 ± 2.1	7.3 ± 2.7	10.6 ± 4.5	<0.001	6.2 ± 4.3

Note: All items calculated as the mean ± sd per weak consumption; ^aP for trend across dairy quartiles in each study year; ^bFat milk and yoghurt, cream (per weak); ^cMilk, yoghurt and cheese (per weak)

Table 3 show the association between types of dairy products intake (total dairy, low-fat dairy and high-fat dairy) with risk of major cardiovascular events. We consider zero consumption as a reference category [11]. the analysis based on the quartiles of dairy products (per week) showed that higher intake of total dairy (>5 servings per week) was associated with lower risk of CVD (HR 0.75; 95% CI 0.53-0.99; p trend=0.02), and average consumption of total dairy (3-5 servings per week) versus zero intake was associated with lower risk of stroke (HR 0.35; 95%

CI 0.15-0.89; p trend=0.05). These results are based on full adjusted model that was additionally adjusted by clinical status like HDL, LDL, blood pressure, diabetes mellitus and BMI. None of the previous models, including the crude model, showed significant results [12].

Table 3: Adjusted hazard ratios and 95% confidence intervals for associations between dairy consumption and cardiovascular disease.

	Dairy quartiles				P trend ^a	
	1 st	2 nd	3 rd	4 th		
Total dairy	CVD	HR (95% CI)				
	Model 1	1	0.65 (0.34-1.22)	0.73 (0.46-1.15)	0.84 (0.59-1.17)	0.582
	Model 2	1	0.60 (0.32-1.13)	0.72 (0.45-1.14)	0.78 (0.56-1.10)	0.429
	Model 3	1	0.60 (0.32-1.13)	0.72 (0.45-1.14)	0.78 (0.56-1.10)	0.433
	Model 4	1	0.58 (0.31-1.09)	0.72 (0.45-1.14)	0.77 (0.54-1.08)	0.095
Model 5	1	0.65 (0.47-0.91)	0.47 (0.55-0.99)	0.75 (0.53-0.99)	0.02	
IHD	Model 1	1	0.70 (0.21-2.38)	0.89 (0.37-2.13)	0.94 (0.50-1.76)	0.917
	Model 2	1	0.68 (0.20-2.32)	0.95 (0.40-2.29)	0.94 (0.50-1.70)	0.804
	Model 3	1	0.64 (0.19-2.19)	0.89 (0.37-2.14)	0.90 (0.48-1.70)	0.83

	Model 4	1	0.64 (0.19-2.20)	0.87 (0.36-2.08)	0.88 (0.47-1.67)	0.852	
	Model 5	1	0.50 (0.14-1.75)	0.71 (0.29-1.74)	0.87 (0.46-1.66)	0.709	
	Stroke						
	Model 1	1	0.76 (0.15-1.44)	0.50 (0.14-1.72)	0.60 (0.23-1.55)	0.441	
	Model 2	1	0.70 (0.14-3.62)	0.48 (0.14-1.65)	0.56 (0.21-1.45)	0.406	
	Model 3	1	0.70 (0.13-3.60)	0.44 (0.13-1.54)	0.55 (0.21-1.44)	0.334	
	Model 4	1	0.56 (0.11-2.97)	0.39 (0.11-1.38)	0.49 (0.19-1.30)	0.288	
	Model 5	1	0.44 (0.19-0.99)	0.35 (0.15-0.89)	0.51 (0.21-1.22)	0.05	
Low fat dairy	CVD						
	Model 1	1	0.67 (0.36-1.26)	0.75 (0.47-1.19)	0.90 (0.65-1.26)	0.215	
	Model 2	1	0.70 (0.37-1.30)	0.80 (0.50-1.27)	0.92 (0.66-1.28)	0.258	
	Model 3	1	0.68 (0.37-1.24)	0.80 (0.51-1.26)	0.84 (0.60-1.17)	0.173	
	Model 4	1	0.65 (0.36-1.20)	0.79 (0.50-1.25)	0.83 (0.60-1.16)	0.14	
	Model 5	1	0.51 (0.28-0.95)	0.64 (0.40-0.98)	0.74 (0.52-1.03)	0.03	
	IHD						
	Model 1	1	0.40 (0.07-1.16)	0.48 (0.09-2.61)	0.85 (0.10-1.95)	0.7	
	Model 2	1	0.39 (0.07-1.10)	0.42 (0.08-2.30)	0.95 (0.12-1.75)	0.67	
	Model 3	1	0.86 (0.28-1.68)	0.99 (0.08-2.36)	0.95 (0.51-1.76)	0.666	
	Model 4	1	0.84 (0.27-1.64)	0.98 (0.41-2.33)	0.95 (0.51-1.78)	0.979	
	Model 5	1	0.66 (0.21-1.10)	0.79 (0.33-1.89)	0.80 (0.33-1.89)	0.938	
	Stroke						
	Model 1	1	0.54 (0.15-1.97)	0.79 (0.31-1.75)	0.89 (0.17-1.53)	0.601	
	Model 2	1	0.52 (0.14-1.92)	0.74 (0.29-1.87)	0.80 (0.15-2.08)	0.599	
	Model 3	1	0.87 (0.18-1.36)	0.62 (0.17-2.24)	0.75 (0.29-1.91)	0.548	
	Model 4	1	0.73 (0.14-1.74)	0.55 (0.15-2.02)	0.41 (0.10-1.62)	0.466	
	Model 5	1	0.44 (0.08-1.50)	0.41 (0.10-1.62)	0.61 (0.24-1.56)	0.207	
	High fat dairy	CVD					
		Model 1	1	0.85 (0.58-1.25)	0.98 (0.57-1.68)	0.91 (0.47-1.79)	0.76
Model 2		1	0.76 (0.52-1.11)	0.94 (0.55-1.60)	0.86 (0.44-1.68)	0.353	
Model 3		1	0.71 (0.55-0.91)	0.86 (0.62-1.19)	0.75 (0.52-1.08)	0.045	
Model 4		1	0.71 (0.55-0.92)	0.86 (0.62-1.04)	0.77 (0.54-1.01)	0.04	
Model 5		1	0.80 (0.62-0.98)	0.90 (0.65-1.26)	0.84 (0.58-1.02)	0.03	
IHD							
Model 1		1	0.79 (0.39-1.58)	0.93 (0.35-1.52)	1.78 (0.58-2.46)	0.127	
Model 2		1	0.93 (0.46-1.87)	0.98 (0.41-1.96)	1.9 (0.65-2.10)	0.236	
Model 3		1	0.75 (0.46-1.20)	0.74 (0.39-1.43)	1.26 (0.72-1.21)	0.32	
Model 4		1	0.75 (0.36-1.21)	0.74 (0.38-1.42)	1.27 (0.72-2.24)	0.31	
Model 5		1	0.87 (0.53-1.41)	0.85 (0.44-1.64)	1.26 (0.81-2.53)	0.434	
Stroke							
Model 1		1	0.27 (0.08-0.85)	0.70 (0.18-1.76)	0.74 (0.13-1.99)	0.075	
Model 2		1	0.28 (0.09-0.89)	0.75 (0.19-1.97)	0.74 (0.13-1.08)	0.094	
Model 3		1	0.34 (0.14-0.85)	0.72 (0.32-0.84)	0.77 (0.35-1.05)	0.02	
Model 4		1	0.33 (0.40-0.92)	0.73 (0.18-0.99)	0.71 (0.48-1.63)	0.02	
Model 5		1	0.35 (0.14-0.86)	0.67 (0.42-0.89)	0.97 (0.46-1.47)	0.04	

Note: CVD: Cardiovascular Disease; IHD: Ischemic Heart Disease (myocardial infarction, unstable angina, sudden cardiac death); Model 1: Crude model; Model 2: Adjusted by age, gender and education; Model 3: Additionally, adjusted by physical activity, smoking status, stress and family history of CVD; Model 4: Additionally, adjusted by consumption of fruits, vegetable, sweets, solid oil, liquid oil and fast food; Model 5: Additionally, adjusted by HDL, LDL, blood pressure, diabetes mellitus and BMI; aThe dairy intake was used as a continuous variable in the models

About high fat dairy, intake of 3-5 servings per week compared with zero intake, was associated with lower risk of stroke (HR 0.67; 95% CI 0.42-0.89; p trend=0.04) and similar associations were observed in second quartile (<3 servings per week) (HR 0.35; 95% CI 0.14-0.86; p trend=0.04) [13]. Also lower risk of CVD was observed in consumption of <3 servings per week versus zero intake (HR 0.80; 95% CI 0.62-0.98; p trend=0.03). Except for the crude model and model adjusted by age, gender and education (Model 2), other models showed <3 servings per week of high-fat dairy can reduce risk of CVD significantly. The results are reported based on full adjusted model (Model 5). Three-five serving of low-fat dairy per week, only reduced the risk of CVD (HR 0.64; 95% CI 0.40-0.98; p trend=0.03), and similarly for intake of <3 servings per week (HR 0.51; 95% CI 0.28-0.95; p trend=0.03) compared with zero intake [14].

DISCUSSION

In this large, prospective cohort study involving participants among Iranian population during 13 years of follow up, we examined the relationship between dairy intake patterns and risk of cardiovascular disease events. Three major dairy patterns were identified in three phases: Total dairy, low fat and high fat dairy. The result showed that higher intake of total dairy was associated with lower risk of CVD and average consumption of total dairy versus zero intake was associated with lower risk of stroke [15]. About high fat dairy, intake of 3-5 servings per week compared with zero intake, was associated with lower risk of stroke, and risk of CVD was lower with consumption of high-fat dairy for <3 servings per week. Low fat dairy only reduced the risk of CVD. No association was found between dairy consumption and IHD. Our findings support that consumption of dairy products might be beneficial for cardiovascular disease, especially for CVD event.

Dairy products are a various food group that include fermented and cultured products may be beneficial to cardiovascular health. They have many different nutrients and rich source of minerals, such as Ca, K and Mg; vitamins, such as riboflavin, vitamin D and B12; and protein, such as whey and casein. Vitamin D; improve blood lipid profile, increase insulin sensitivity and control blood pressure *via* the regulation of the renin angiotensin aldosterone system. Calcium; improve blood lipid profile and inhibit fat absorption by binding with fatty acids to form insoluble soaps. Potassium, magnesium and phosphorus are good for reduction, control and management of blood pressure [16]. Protein and bioactive peptides; increase in satiety levels and reduce blood pressure through the inhibit the angiotensin-1 converting enzyme. The milk proteins have also beneficial effects on oxidative stress and inflammation. Other bioactive molecules in dairy products can fuel intestinal alkaline phosphatase, an endogenous anti-inflammatory enzyme interaction, of all these nutrient sources may have a desirable effect on CVD.

Dairy fatty acids contain medium chain and branched chain fatty acids, and their effect on health might differ from saturated fat in meat and processed meats. And they good for weight management *via* the inhibition of abiogenesis and the regulation of lipogenesis, improvement of blood lipid profile, increase in

insulin sensitivity and glucose tolerance and anti-inflammatory effect [17].

Dairy especially high fat dairy, content Saturated Fat (SFA) and fat has more calories so getting more saturated fat, raises LDL cholesterol and that's the number one risk factor for heart disease. Because of this some people avoid dairy especially high fat dairy. However recent findings have indicated relationship between SFA and cardiovascular events more clear previously assumed. Recent research indicates that dairy products have a neutral or even a positive effect on cardiovascular health contrary to previous assumptions.

There are some meta-analyses of cohort studies that their results are close to our findings. For example, a meta-analysis reported about lower risk of cardiovascular disease and lower risk of stroke with higher dairy consumption, and in another meta-analysis, it is shown that full fat dairy intake was associated inversely and significantly with stroke and intake of total dairy was associated significantly and inversely with stroke. The study found inverse associations of full fat dairy intake and CVD, similar to the result we reached in our study. On the contrary, there are meta-analysis that showed different results than us. There was a meta-analysis on 29 prospective cohort studies that has shown all kinds of dairy consumption (total dairy, high and low fat dairy) has no effect on CHD or CVD [18]. This meta-analysis included cohort studies that had examined the consumption of high fat and low fat butter and cheese as high fat and low fat dairy or studies that looked at the effects of some dairy products, such as milk and cheese, on the side of nutrition. While in our study, we examined all types of dairy products including milk (high fat and low fat), cheese (high fat and low fat), cream and yogurt (high fat and low fat). And we subdivided into three groups of high fat, low fat and regular dairy by factor analysis. We also divided each of the three dairy groups (total dairy, high fat and low fat dairy) into four categories based on their weekly consumption.

There was a meta-analysis that examined the relationship between dairy consumption and stroke. In this study, only the relationship between cheese and milk intake was investigated and the inverse relationship between cheese and milk intake and stroke was found. Many cohort studies have examined the relationship between dairy and heart disease, but some of them have only examined some dairy icons such as milk and/or cheese. In some studies, have only evaluated one of the outcome of CVD, IHD and/or stroke and in some of them there was no classification based on the amount of consumption.

One of the cohort studies that was almost similar to our studies, conducted in 2013 for 13 years follow-up to measure this relationship across all three categories of dairy products. However, this study only assessed the outcome of a stroke, and they found that dairy products had no effect on stroke. In our study we conducted 13 years follow-up and examined this relationship based on weekly dairy intake and by additionally account some influential factors such as HDL, LDL, blood pressure, diabetes mellitus and family history of CVD that this study did not adjusted by these variables. In addition, our results showed that medium intake of high-fat dairy and total dairy products (3-5 servings per week) significantly reduces stroke [19].

Similar to our results, other studies have shown the association between dairy consumption and stroke. But there was a cohort studies in 21 countries conducted in 2018 that examined association of dairy intake with cardiovascular disease and mortality. The study examined the relationship between total dairy and specific types of dairy products like: Milk, cheese, butter and yogurt separately, with cardiovascular mortality, major cardiovascular disease and stroke. The result showed that higher intake of total dairy was associated with a lower risk of cardiovascular disease and stroke [20].

Overall, our research is the only cohort study that examine the relationship between the most consumed dairy products (milk, cheese, yogurt and cream) in the form of three groups of high fat, low fat and total dairy with all three major outcomes including CVD, stroke and IHD. Five models were used to evaluate this relationship. In each model, a number of influential factors were entered into the model and their impact on the relationship was evaluated [21]. We divided the weekly intake of dairy products from low to high in four categories, and therefore evaluated the impact of each level of dairy consumption on cardiac events. Also we examined and tested the behavior of individuals in each category. For example, in the group with the highest intake of dairy products (weekly), the level of mental health problems (stress, depression, anxiety) was lower and doing physical activity was higher. Or the consumption of fruit and vegetable were significantly higher in those who consumed more dairy. And eventually, people who consumed more dairy products significantly more tended to consume liquid oil than solid oils [22].

CONCLUSION

Consequently, the reason that our results were different from results of some studies may be due to these factors. Because all of these important factors such as having no mental problems, doing physical activity, consuming fruits and vegetables to provide the body necessary vitamins, and consuming liquid oil instead of solids, are associated with heart and brain health. So consuming dairy in addition to these can prevent heart attacks and strokes. The results suggest that dairy fat also, contrary to popular belief, does not increase the risk of heart disease and fatty acid present in dairy may lower risk of cardiovascular disease, particularly from stroke and CVD.

ACKNOWLEDGEMENT

The ICRC affiliated with the Isfahan university of medical sciences has been conducted this cohort study. Our sincere appreciation goes to the team of the ICRC and Isfahan provincial health center. The authors also would like to thank all of the participants.

CONFLICT OF INTERESTS

The authors declare that they have no potential conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. All authors participated in the manuscript preparation,

read and approved the final version of the manuscript submitted for publication.

FUNDING

RK collecting and analysing the data and drafting the manuscript. Sh.H.J and RH helped to design and administer the questionnaire and improve the manuscript. HR and MS contributed to design the study. NM interpret the results and improve the manuscript. MM supervised all phases of study, design, data analysis and manuscript development. NS conducted the study, data collecting and designing.

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