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Overview of Meta-Analyses: The Impact of Lifestyle on Stroke Risk

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ABSTRACT

Stroke is one of the most prevalent cardiovascular diseases worldwide, both in high-income countries and in medium and low-medium income countries. The WHO report on non-communicable diseases (NCDs) indicates that the highest behavioral risk in NCDs is attributable to incorrect nutrition. The objective of our work is to present an overview of meta-analyses that have investigated the impact of different foods and / or drinks in relationship with the risk of stroke events (ischemic/ hemorrhagic). The papers to be included in the overview were sought in the MEDLINE, EMBASE, Scopus, Clinicaltrials.gov, Web of Science, and Cochrane Library and were selected according to PRIMA flow chart. Quality assessment were made according to AMSTAR scale. This overview shows that all primary studies came from countries with high income level. This evidence shows that many countries are not represented. Therefore, different lifestyles, ethnic groups, potentially harmful or virtuous eating habits are not reported. It is important to underline how the choose of foods may help reduce the risk of cardiovascular diseases and stroke in particular.

Key-words: overview, meta-analyses, stroke, nutrition, geographical areas

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INTRODUCTION

Stroke is one of the most prevalent cardiovascular diseases worldwide. It is estimated that in 2010 there were 11.569.538 ischemic stroke events, 63% of which were in countries medium and low-medium income countries [1]. In the same year, 5.324.997 of hemorrhagic stroke occurred, 80% of which were in medium and low-medium income areas [1]. This difference is similar for mortality, which is significantly lower in high-income countries compared to those of middle/medium-low [1]. It is estimated that in Europe the costs of the disease are around €7775 per patient, with a total cost, in billions, of 64.053 euros [2]. In the United States in 2008 the global costs were estimated to be 62.5 billion dollars, the expenditure forecast to 2050 is about 2.2 trillion dollars until 2050 [3].

The WHO report on non-communicable diseases (NCDs) indicates that the highest behavioral risk is attributable to incorrect nutrition, particularly in the WHO European region [4].

Numerous meta-analysis studies have been conducted to evaluate the relationship between diet and stroke risk. A meta-analysis of Alexander et al. [5], seems to indicate a protective action resulting from the consumption of cheese. This data is in line with Briggs et al. [6]. Dairy products should probably be consumed as part of a balanced diet in which there is adequate intake of all nutrients within an appropriate calorie count [7-10].

Regarding alcohol use and/or abuse [8,11], red wine contains polyphenols, including resveratrol, a molecule with not only cardio protective pleiotropic effects, but also neuroprotective, anti-microbial and anti-angiogenetic. All this has a positive influence on the prevention of ischemic stroke since it acts on one of the main causes, atrial fibrillation [12]. The same may be extended to moderate consumption of beer [13].

Mono-unsaturated [14] and poly-unsaturated [15] have been considered a valid nutritional support able to positively modify lipid structure in patients [16].

In addition, it is important to underline consumption of fruit and vegetables [17]. The Centre for Disease Control and Prevention guidelines recommend the daily consumption of 1.5-2.0 cups of fruit and 2.0-3.0 cups of vegetables [18].

Consumption of nuts could have a protective role on the decrease cardiovascular disease [19, 20]. The benefit of the intake of nuts seems to be linked to the composition of PUFA fatty acids that improve the performance of the cardiovascular system as reported by Del Gobbo et al. [21].

Finally, the increased risk of ischemic stroke in women who consume high quantities of sugary drinks is due to the insulin peak resulting in the ingestion of large amounts of glucose [22]. Furthermore, it is important to take into consideration how many of these drinks contain added fructose. Fructose enters the glycolytic pathway down-regulating it with the intermediate products of its metabolism [glycerol 3-phosphate and acetyl CoA], thus favoring lipogenesis and accumulation of intramuscular and visceral fat [23].

Tea [24] seems to have a role in stroke prevention, as reported by Arab and colleagues as well as folic acid [25-27]. The consumption of whole grains does not present significant results [28].

The objective of our work is to present an overview of meta-analyses that have investigated the impact of different foods and / or drinks in relationship with the risk of stroke events (ischemic/ hemorrhagic). We considered the meta-analyses based on: cohort studies and randomized clinical trials.

MATERIALS AND METHODS

Meta-analyses regarding the onset of hemorrhagic and/or ischemic strokes in subjects following dietary regimes with a given food or specific nutritional or nutraceutical support have been considered. In addition, studies investigating secondary prevention of strokes were considered, also in relation to a specific food or nutritional or nutraceutical support.

The papers included in the overview were sought in the last 10 years in the MEDLINE, EMBASE, Scopus, Clinicaltrials.gov, Web of Science, and Cochrane Library databases up to 31 December 2018. The search strategy was conducted using the following terms: Stroke OR Strokes OR CVA Cerebrovascular Accident OR CVAs [Cerebrovascular Accident] OR Cerebrovascular Apoplexy, Cerebrovascular OR Vascular Accident, Brain OR Brain Vascular Accident OR Brain Vascular

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Accidents OR Vascular Accidents OR Brain OR Cerebrovascular Stroke OR Cerebrovascular Strokes OR Stroke, Cerebrovascular OR Strokes, Cerebrovascular OR Apoplexy OR Cerebral Stroke OR Cerebral Strokes OR Stroke, Cerebral OR Strokes, Cerebral OR Stroke, Acute OR Acute Stroke OR Acute Strokes OR Strokes, Acute OR Cerebrovascular Accident Acute OR Acute Cerebrovascular Accident OR Acute Cerebrovascular Accidents OR Cerebrovascular Accidents, Acute)) AND "Food"[Mesh]) AND "Meta-Analysis" [Publication Type]. The selection of the works was conducted using the PRISMA method [29] by two-blinded authors (P.M.A. and L.R.). A methodologist (E.A.) resolved any disagreements.

Table 1 shows the studies by author and by food considered with the respective dose effects found.

Table 1. Characteristics of included meta-analyses in the overview according to food or beverage, study design and type of stroke

Author	Food or beveraage	Control group	Literature search-update	Number of primary studies	Type of strokes	Number of Studies for evaluated strokes	Population		Effect size 95% C.I.
							N. tot	N. events	
Cohort studies									
Alexander [5]	High milk intake	Low milk intake	2016	K=31	Ischemic or Hemorrhagic	7	-	-	0.91 (0.83; 0.99)
	High milk intake	Low milk intake			Ischemic or Hemorrhagic (in men)	4	-	-	1.04 (0.96; 1.14)
	High milk intake	Low milk intake			Ischemic or Hemorrhagic	4	-	-	0.93 (0.81; 1.06)
	High milk intake	Low milk intake			Hemorrhagic	3	-	-	0.93 (0.69; 1.25)
	High cheese intake	Low cheese intake			Ischemic or Hemorrhagic	4	-	-	0.87 (0.77; 0.99)
Zhang [8]	Western dietary pattern - High categories #	Western dietary pattern - low categories #	2015	K=21	Ischemic or Hemorrhagic	8	143798	2049	1.05 (0.82; 1,35) **
	Healthy dietary pattern - High categories #	Healthy dietary pattern - low categories #				14	318813	3971	0.77 (0.64; 0.93) **
Mullie [9]	200 ml/d Daily milk consumption	No milk consumption	2016	K=19	Ischemic or Hemorrhagic	10	567717	39352	0.91 (0.82; 1.02)
					Ischemic or Hemorrhagic (in men)	5	-	-	0.96 (0.86; 1.09)
Pimpin [10]	Butter intake <14g/d	Butter intake >14g/d	2016	K=4	Ischemic or Hemorrhagic	3	173853	5229	1.01 (0.98; 1.03)
Larsson [11]	Light-moderate drinking s	No drinkers	2016	K=27	Ischemic stroke	8	-	-	0.87 (0.81; 0.92)
	Heavy drinking	No drinkers				8	-	-	1.13 (0.95; 1.19)
	Light-moderate drinking	Never drinkers				8	-	-	0.87 (0.82; 0.91)

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	Heavy drinking	Never drinkers				8	-	-	1.06 (0.95; 1.19)
	Occasional drinkers drinking	Light-moderate				8	-	-	0.98 (0.94;1.04)
	Heavy drinking	Occasional drinkers				8	-	-	1.13 (1.03; 1.24)
	Light-moderate drinking	No drinkers			Intracerebral hemorrhage	5	-	-	0.91 (0.64; 1.29)
	Heavy drinking	No drinkers				4	-	-	1.21 (0.87; 1.67)
	Light-moderate drinking	Occasional drinkers				4	-	-	1.04 (0.89; 1.21)
	Heavy drinking	Occasional drinkers				4	-	-	1.74 (1.45;2.09)
	Light-moderate drinking	No drinkers			Subarachnoid Hemorrhage events	5	-	-	1.39 (1.00;1.92)
	Heavy drinking	No drinkers				3	-	-	1.43 (1.00; 2.05)
	Light-moderate drinking	Occasional drinkers				4	-	-	1.10 (0.84; 1.44)
	Heavy drinking	Occasional drinkers				4	-	-	1.62 (0.89;2.29)
Cheng [14]	High monounsaturated fatty acid intake (MUFAs)	Low usage of MUFA	2016	K=10	Ischemic or Hemorrhagic	10	314511	5827	0.86 (0.74; 1.00)
					Ischemic stroke	8		-	0.92 (0.79; 1.08)
					Hemorrhagic stroke	5	-	-	0.68 (0.49; 0.96)
Larsson [15]	High long-chain omega-3 polyunsaturated fatty acids (PUFAs) intake	Low intake of PUFA	2012	K=10	Ischemic or Hemorrhagic	10	242076	5238	0.90 (0.81; 1.10)
					Ischemic stroke	5	-	-	0.82 (0.71; 0.94)
					Hemorrhagic stroke	5	-	-	0.80 (0.55; 1.15)
Aune [17]	High intake of fruit and vegetables	Low intake of fruit and vegetables	2017	K=95	Ischemic or Hemorrhagic	8	226910	10560	0.79 (0.71; 0.88)
	High intake of fruit	Low intake of fruit			Ischemic or Hemorrhagic	17	960337	46951	0.82 (0.77; 0.87)

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	High intake vegetables	Low intake vegetables			Ischemic or Hemorrhagic	13	427124	14519	0.87 (0.81; 0.95)
	High intake Apples, pears	Low intake Apples, pears			Ischemic or Hemorrhagic	6	-	-	0.88 (0.81; 0.96)
	High intake berries	Low intake berries			Ischemic or Hemorrhagic	5	-	-	0.98 (0.86; 1.12)
	High intake Citrus Fruits	Low intake Citrus Fruits			Ischemic or Hemorrhagic	8	-	-	0.74 (0.65; 0.84)
	High intake Citrus Fruits juice	Low intake Citrus Fruits juice			Ischemic or Hemorrhagic	2	-	-	0.90 (0.74; 1.10)
	High intake Dried fruits	Low intake Dried fruits			Ischemic or Hemorrhagic	2	-	-	0.92 (0.74; 1.15)
	High intake Fruits juice	Low intake Fruits juice			Ischemic or Hemorrhagic	2	-	-	0.67 (0.60; 0.76)
	High intake Grapes	Low intake Grapes			Ischemic or Hemorrhagic	2	-	-	0.72 (0.47; 1.10)
	High intake Allium vegetables	Low intake Allium vegetables			Ischemic or Hemorrhagic	2	-	-	0.89 (0.80; 1.00)
	High intake Cruciferous vegetables	Low intake Cruciferous vegetables			Ischemic or Hemorrhagic	4	-	-	0.97 (0.78; 1.20)
	High intake Green leafy vegetables	Low intake Green leafy vegetables			Ischemic or Hemorrhagic	4	-	-	0.88 (0.81; 0.95)
	High intake Pickled vegetables	Low intake Pickled vegetables			Ischemic or Hemorrhagic	2	-	-	0.80 (0.73; 0.88)
	High intake Potatoes	Low intake Potatoes			Ischemic or Hemorrhagic	4	-	-	0.94 (0.87; 1.01)
	High intake Root vegetables	Low intake Root vegetables			Ischemic or Hemorrhagic	2	-	-	1.01 (0.89; 1.14)
	High intake Tomatoes	Low intake Tomatoes			Ischemic or Hemorrhagic	3	-	-	0.95 (0.68; 1.31)
	High intake Berries	Low intake Berries			Ischemic	3	-	-	0.95 (0.75; 1.21)
	High intake Citrus fruits	Low intake Citrus fruits			Ischemic	7	-	-	0.78 (0.66; 0.92)
	High intake Citrus Fruits juice	Low intake Citrus Fruits juice			Ischemic	2	-	-	0.65 (0.51; 0.84)
	High intake Allium vegetables	Low intake Allium vegetables			Ischemic	2	-	-	0.90 (0.78; 1.03)

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	High intake Cruciferous vegetables	Low intake Cruciferous vegetables			Ischemic	5	-	-	0.82 (0.66; 1.01)
	High intake Green leafy vegetables	Low intake Green leafy vegetables			Ischemic	4	-	-	0.88 (0.78; 0.99)
	High intake Potatoes	Low intake Potatoes			Ischemic	5	-	-	0.97 (0.87; 1.08)
	High intake Root vegetables	Low intake Root vegetables			Ischemic	3	-	-	0.93 (0.73; 1.18)
	High intake Tomatoes	Low intake Tomatoes			Ischemic	2	-	-	0.80 (0.69; 0.92)
	High intake Berries	Low intake Berries			Hemorrhagic	3	-	-	1.15 (0.89; 1.49)
	High intake Citrus fruits	Low intake Citrus fruits			Hemorrhagic	3	-	-	0.74 (0.55; 1.01)
	High intake Cruciferous vegetables	Low intake Cruciferous vegetables			Hemorrhagic	2	-	-	0.83 (0.33; 2.12)
	High intake Potatoes	Low intake Potatoes			Hemorrhagic stroke	3	-	-	1.06 (0.83; 1.36)
	High intake Root vegetables	Low intake Root vegetables			Hemorrhagic stroke	2	-	-	1.05 (0.76; 1.44)
Chen [19]	All nuts high consumption	All nuts low consumption	2017	K=16	Ischemic or Hemorrhagic	12	449293	4398	0.82 (0.73; 0.91)
	Nut plus peanut butter high consumption	Nut plus peanut butter low consumption				3	104531	924	0.84 (0.70; 1.01)
	Peanuts high consumption	Peanuts low consumption				5	265252	7025	0.76 (0.69; 0.82)
	Tree nuts high consumption	Tree nuts low consumption				3	130987	6394	0.79 (0.68; 0.92)
Aune [28]	High Intake of whole grains or specific types of grains	low Intake of whole grains or specific types of grains	2016	K=15	Ischemic or Hemorrhagic	5	-	-	0.87 (0.72; 1.05)
	High intake Whole grain bread	Low intake Whole grain bread				2	-	-	0.88 (0.75; 1.03)
	High intake of whole grain breakfast cereals	Low intake of whole grain breakfast cereals				2	-	-	0.99 (0.53; 1.86)

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	High intake of refined grain	Low intake of refined grain				4	-	-	0.95 (0.78; 1.14)
	High intake total rice	Low intake total rice				4	-	-	1.02 (0.94; 1.11)
Wu [31]	High yogurt intake	Low yogurt intake	2017	K=7	Ischemic or Hemorrhagic	7	-	-	1.02 (0.92; 1.13)
Muto [36]	High saturated fatty acid intake	Low saturated fatty acid intake	2018	K=16	Ischemic	11	-	-	0.88 (0.81; 0.96)
Narain [38]	High intake sugar-sweetened beverage	Low intake sugar-sweetened beverage	2016	K=7	Ischemic or Hemorrhagic	3	236061	-	1.10 (0.97; 1.25)
	High intake sugar-sweetened beverage	Low intake sugar-sweetened beverage			Ischemic stroke (in men)	3	-	-	1.01 (0.74; 1.37)
	High intake sugar-sweetened beverage	Low intake sugar-sweetened beverage			Ischemic stroke (in women)	3	-	-	1.33 (1.07; 1.66)
	High intake sugar-sweetened beverage	Low intake sugar-sweetened beverage			Hemorrhagic stroke (in men)	3	-	-	0.87 (0.68; 1.12)
	High intake sugar-sweetened beverage	Low intake sugar-sweetened beverage			Hemorrhagic stroke (in women)	3	-	-	0.83 (0.62; 1.10)
Cai [39]	Glycemic index	-	2014	K=7	Ischemic or Hemorrhagic	7	-	-	1.10 (0.99; 1.21)
	Glycemic load								1.19 (1.05; 1.36)
	Carbohydrate intake								1.12 (0.93; 1.35)
Yan [40]	High soy consumption	Low soy consumption	2016	K=11	Ischemic or Hemorrhagic	11	-	-	0.82 (0.68; 0.99)
Zhang [41]	High fiber intake	Low fiber intake	2013	K=11	Ischemic or Hemorrhagic	11	325627	-	0.83 (0.74; 0.93)

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					Ischemic	8	-	-	0.83 (0.74; 0.93)
					Hemorrhagic	5	-	-	0.87 (0.74; 1.05)
Tang [42]	High flavonoids intake	Low flavonoids intake	2016	K=11	Ischemic or Hemorrhagic	11	-		0.89 (0.82; 0.97)
Zhang [43]	Protein intake	-	2016	K=12	Ischemic or hemorrhagic	12			0.98 (0.89; 1.07)
					Ischemic	8			0.94 (0.80; 1.10)
					Hemorrhagic	4	-	-	1.05 (0.97; 1.14)
	Animal protein	-			Ischemic or Hemorrhagic	8			0.94 (0.75; 1.17)
	Vegetable protein	-			Ischemic or Hemorrhagic	8			0.90 (0.82; 0.99)
Qin [44]	Lean fish	Fatty fish	2018	K=5	Ischemic or Hemorrhagic	5	-	-	0.88 (0.74; 1.04)
	High lean fish intake	Low lean fish intake	2018	K=5	Ischemic or Hemorrhagic	5	-	-	0.81 (0.67; 0.99)
Xun [45]	High fish intake	Low fish intake	2012	K=16	Ischemic or Hemorrhagic	16	-	-	0.91 (0.85; 0.98)*
Kim [46]	High total meat intake	Low total meat intake	2016	K= 7	Ischemic or Hemorrhagic	6	-	-	1.18 (1.09; 1.28)
	High red meat intake	Low red meat intake				7	-	-	1.11 (1.03; 1.20)
	High processed meat intake	Low processed meat intake				8	-	-	1.17 (1.08; 1.25)
	High white meat intake	Low white meat intake				4	-	-	0.87 (0.78; 0.96)
Yuan [47]	High chocolate intake	low chocolate intake	2017	K=8	Ischemic or Hemorrhagic	8	-	-	0.84 (0.78; 0.90)
Chen [48]	High C-vitamin intake	Low C-vitamin intake	2011	K=11	Ischemic or Hemorrhagic	11	-	-	0.81 (0.74; 0.90)
					Ischemic	4			0.77 (0.64; 0.92)
					Hemorrhagic	2	-	-	1.07 (0.38; 3.00)
Afshin [49]	Legumen 100 gr/week	No consumption	2014	K=6	Ischemic	3	-	-	1.07 (0.77; 1.50),
					Hemorrhagic	4	-	-	1.23 (0.91; 1.66)

Alexander [50]	1 egg/day	< 2 eggs/week	2016	K=7	Ischemic or Hemorrhagic	7	-	-	0.88 (0.81; 0.97)
Martin-Gonzales [51]	Olive oil (>25 g)	Olive oil (<25 g)	2014	K=2	Ischemic or Hemorrhagic	2	-	-	0.74 (0.60; 0.92)
Cheng [53]	Vitamin E	-	2018	K=9	Ischemic or Hemorrhagic	9	-	-	0.83 (0.73; 0.94)
RTC									
Bolland [22]	High Ca from dairy products	Low Ca from dairy products	2011	K=8	Ischemic or Hemorrhagic	5	-	-	0.69 (0.60; 0.81)
	Calcium supplement 500 mg and D vitamin	Placebo			Ischemic or Hemorrhagic	3	20090	477	1.20 (1.00; 1.43)
Tian [25]	Intervention regimen FA ** only	No supplementation	2017	K=11	Ischemic or Hemorrhagic	11	21295	657	0.79 (0.68; 0.92)
	Intervention regimen FA+B vitamins	No supplementation					27486	1,589	0.91 (0.82; 1.00)
Arab [24]	Tea 3 cups	Tea 1 cups	2009	K=9	Ischemic or Hemorrhagic	9	-	-	0.77 0.71; 0.85
Abdelhamid [33]	Long-chain omega-3 polyunsaturated fatty acids (PUFAs): high intake	Low PUFAs intake	2018	K=32	Ischemic or Hemorrhagic	28	89358	1818	1.06 (0.96-1.16)
	Alpha linoneic acid: high intake	Low alpha linoneic acid intake			Ischemic or Hemorrhagic	4	19327	51	1.15 (0.66; 2.01)
Hooper [34]	Low omega 6	High omega 6 intake	2018	K=4	Ischemic or Hemorrhagic	4	3730	54	1.36 (0.45; 4.11)
Abdelhamid [35]	Polyunsaturated fatty acid high intake	Polyunsaturated fatty acid low intake	2018	K=11	Ischemic or Hemorrhagic	11	14724	165	1.06 (0.96; 1.96)
Hooper [37]	Low saturated fatty acid diet	Low saturated fatty acid diet	2015	K=8	Ischemic or Hemorrhagic	8	50952	1125	1.00 (0.89; 1.12)
Bin [52]	Vitamin E	-	2011	K=13	Ischemic or Hemorrhagic	13	166282	-	1.01 (0.96; 1.07)
					Ischemic	-	-	-	1.01 (0.94;1.09)
					Hemorrhagic	-	-	-	1.12 (0.94; 1.33)

*Where not specified, stroke events is in both sexes **.** # Dietary pattern: high intake of all kinds of red and or processed meats, refined grains, sweets, desserts, high-fat dairy products, and high-fat gravy. *OR. ** Folic Acid.

Table 2 shows the studies by author with the dose response analysis. The methodology used is described in Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Flow-Chart (figure 1).

Table 2. Summary of dose response analysis in studies considered

Author	**Food or beverage intake**	**Control intake**	**Type of strokes**	**Evaluated dose for each food or beverage**	**Number of primary studies**	**Effects size (95% C.I.)**
COHORT STUDIES						
Alexander 2015 [5]	Dairy	No	Ischemic or Hemorrhagic	<1.5 serving/day	-	0.92 (0.89; 0.96)
				≥1.5 serving/day	-	0.91 (0.88; 0.95)
	Milk	No		0-1 serving/day	-	0.95 (0.86; 1.04)
				>1 to <2 serving/day	-	0.98 (0.90; 1.06)
				≥2 serving/day	-	1.01 (0.92; 1.11)
	Cheese	No		0-0.5 serving/day	-	1.00 (0.92; 1.07)
				>0.5-1.5 serving/day	-	0.86 (0.75; 0.97)
				>1.5 serving/day	-	0.92 (0.87; 0.97)
	Dairy and Ca	No		0-100 mg/d Ca from dairy product	-	0.91 (0.84; 1.00)
				>100-300 mg/d Ca from dairy product	-	0.67 (0.58; 0.77)
				>300 mg/d Ca from dairy product	-	0.82 (0.69; 0.97)
Larsson 2016 [11]	Alcohol consumption	Non-drinkers; never drinkers; occasional drinkers.	Ischemic	<1 drink/day	20	0.90 (0.85; 0.95)
				1-2 drink/day	20	0.92 (0.87; 0.97)
				2-4 drink/day	21	1.08 (1.01; 1.15)
				>4 drink/day	12	1.14 (1.02;1.28)
			Hemorrhagic	<1 drink/day	9	0.92 (0.77; 1.10)
				1-2 drink/day	8	0.99 (0.82; 1.18)
				2-4 drink/day	8	1.25 (0.93; 1.67)
				>4 drink/day	8	1.67 (1.25; 2.23)
			Subarachnoid Hemorrhage	<1 drink/day	9	1.21 (0.96; 1.52)
				1-2 drink/day	6	1.11 (0.80; 1.53)
				2-4 drink/day	9	1.39 (0.94;.2.07)
				>4 drink/day	8	1.82 (1.18; 2.82)
Aune 2017 [17]	Fruit and vegetables	No	Ischemic or Hemorrhagic	200 g/day	15	
						0.92 (0.90; 0.94)

	Fruit	No		200 g/day	24	0.90 (0.86; 0.94)
	Vegetables	No		200 g/day	20	0.84 (0.79; 0.90)
	Apples, pears	No		100 g/day	5	0.94 (0.84; 1.05)
	Berries	No		100 g/day	5	1.07 (0.79; 1.45)
	Citrus Fruits	No		100 g/day	9	0.78 (0.69; 0.90)
	Citrus Fruits juice	No		100 g/day	2	0.89 (0.72; 1.10)
	Dried fruits	No		100 g/day	1	0.75 (0.32; 1.81)
	Fruits juice	No		100 g/day	2	0.72 (0.63; 0.83)
	Grapes	No		100 g/day	2	0.57 (0.34; 0.97)
	Allium vegetables	No		100 g/day	1	0.89 (0.76; 1.04)
	Cruciferous vegetables	No		100 g/day	5	1.04 (0.80; 1.36)
	Green leafy vegetables	No		100 g/day	5	0.73 (0.57; 0.94)
	Pickled vegetables	No		100 g/day	2	0.57 (0.43; 0.74)
	Potatoes	No		100 g/day	4	0.98 (0.94; 1.02)
	Root vegetables	No		100 g/day	2	0.96 (0.78; 1.18)
	Tomatoes	No		100 g/day	4	1.01 (0.96; 1.06)
	Berries	No	Ischemic	100 g/day	3	1.02 (0.61; 1.72)
	Citrus fruits	No		100 g/day	7	0.87 (0.79; 0.95)
	Citrus Fruits juice	No		100 g/day	2	0.87 (0.80; 0.96)
	Allium vegetables	No		100 g/day	2	0.93 (0.77; 1.11)
	Cruciferous vegetables	No		100 g/day	5	0.66 (0.41; 1.07)
	Green leafy vegetables	No		100 g/day	4	0.74 (0.62; 0.89)
	Potatoes	No		100 g/day	5	1.00 (0.95; 1.05)
	Root vegetables	No		100 g/day	3	0.91 (0.64; 1.30)
	Tomatoes	No		100 g/day	2	0.92 (0.86; 0.98)
	Berries	No	Hemorrhagic	100 g/day	3	1.66 (0.91; 3.03)
	Citrus fruits	No		100 g/day	3	0.79 (0.59; 1.06)
	Cruciferous vegetables	No		100 g/day	2	0,27 (0.01; 12.54)
	Potatoes	No		100 g/day	3	1.03 (0.91; 1.16)
	Root vegetables	No		100 g/day	2	1.16 (0.66; 2.02)
Aune 2016 [28]	High Whole grain bread	Low intake Whole grain bread	Ischemic or Hemorrhagic	90 g/day	1	0.88 (0.72; 1.07)
	High intake Whole grain breakfast cereals	Low intake Whole grain breakfast cereals		30 g/day	2	1.07 (0.69; 1.64)
	High intake refined grain	Low intake refined grain		90 g/day	5	0.91 (0.81; 1.02)

	High intake total rice	Low intake total rice		100 g/day	4	1.00 (0.97; 1.03)
	High intake total grains	Low intake total grains		90 g/day	5	0.93 (0.85; 1.02)
Chen [49]	C vitamin		Ischemic or Hemorrhagic	Incremental 100 mg/day	10	0.83 (0.75; 0.93)
Tang [44]	Flavoids		Ischemic or Hemorrhagic	Incremental 100 mg/day	3	0.91 (0.77; 1.08)
RCT						
Tian 2017 [25]	FA*** supplementation	No supplementation	Ischemic or hemorrhagic	<2 mg	-	0.78 (0.68; 0.89)
	FA supplementation	No supplementation		≥2 mg	-	0.96 (0.88; 1.04)
	Daily Vit B12	No supplementation		<0.5 mg	-	0.93 (0.78; 1.10)
	Daily Vit B12	No supplementation		≥0.5 mg	-	0.94 (0.86; 1.03)

*** Folic Acid

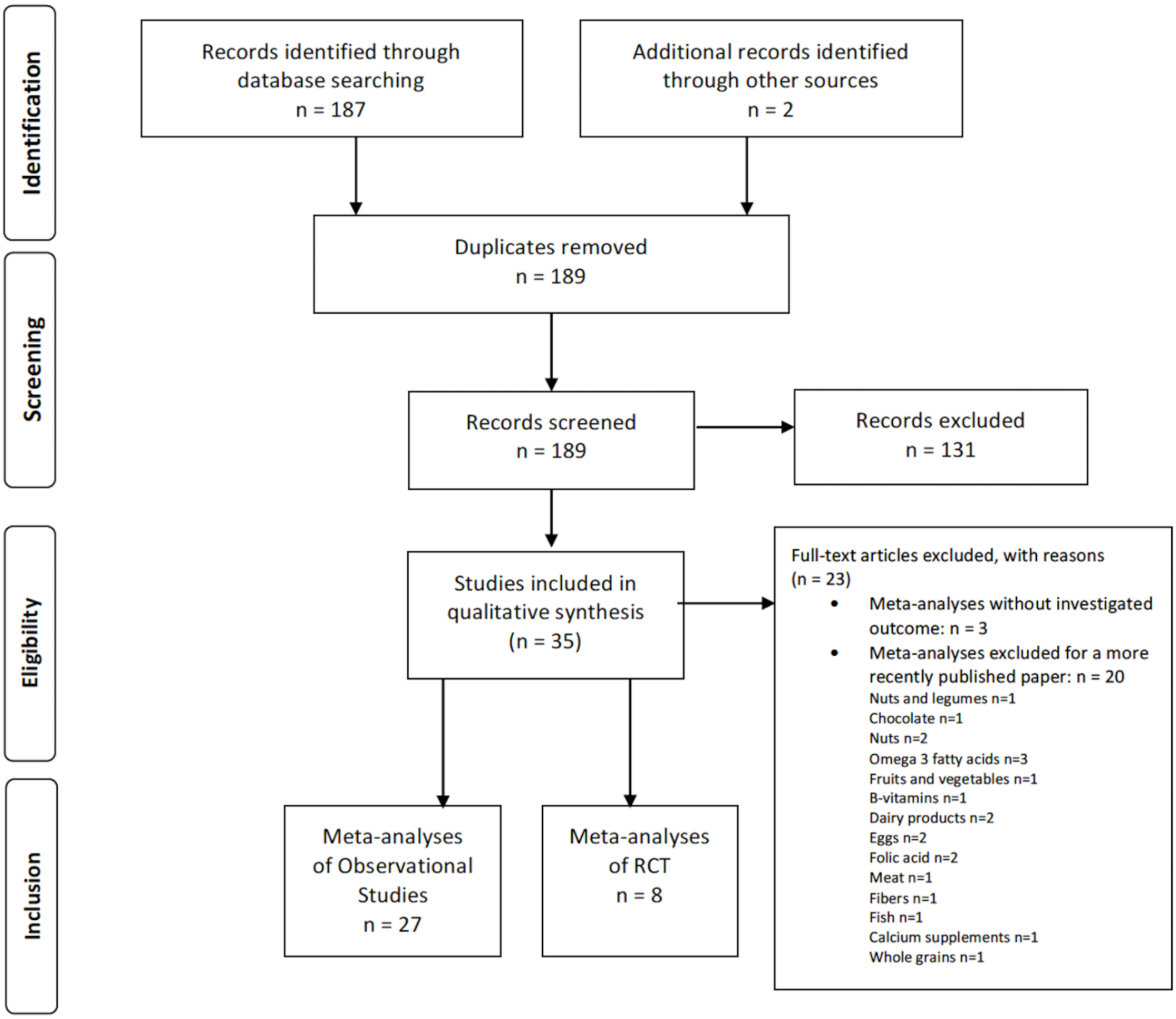

Figure 1. PRISMA Flow-Chart

The quality of the meta-analyses was assessed using the AMSTAR 2 scale by Shea et al. [30] that allows to evaluate the methodological quality of the meta-analyses (Supplementary Table 1). In addition, we evaluated the distribution of primary studies included in each meta-analyses, according to six different geographical areas (Australia, Canada, China Singapore and South Korea, Europe, Japan and USA) and according to four nutritional patterns and/or product type (Eating habits, food, beverage, integration) (figure 2 and table 3).

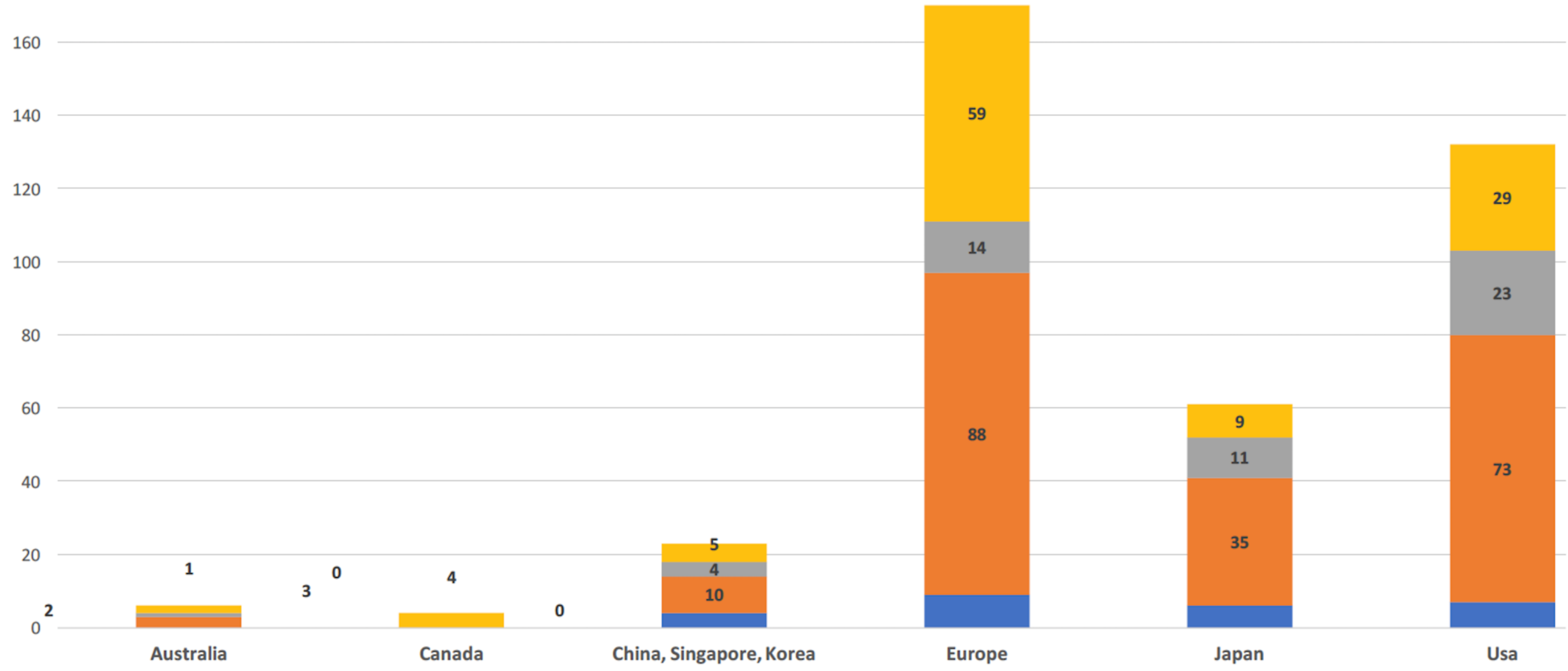

Figure 2. Distribution of primary studies included in meta-analyses considered, according to geographic area and type of nutritional support

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AUSTRALIA		CANADA		CHINA-SINGAPORE-KOREA		EUROPE		JAPAN		USA		LATIN AMERICA	
Food		**Integration**		**Eating habits**		**Eating habits**		**Eating habits**		**Eating habits**		**Integration**	
Omega 3	*1*	*Folic Acid*	*3*	*Healthy diet*	*4*	*Carbohydrates*	*4*	*Healthy diet*	*6*	*Carbohydrates*	*6*	*Omega 3*	*1*
Dried fruits	*2*	*Omega 3*	*1*	**Food**		*Healthy diet*	*5*	**Food**		*Healthy diet*			
Beverage				*Cereals*	*1*	**Food**		*saturated fatty acids*	*5*	**Food**	*4*		
Tea	*1*			*Fibers*	*1*	*Saturated fatty acids*	*2*	*Cereals*	*3*	*Saturated fatty acids*	*2*		
Integration				*Fruits and vegetables*	*3*	*Butter*	*3*	*Chocolate*	*1*	*Meat*	*5*		
Polynsatured fatty acid	*1*			*Dried fruits*	*1*	*Meat*	*4*	*Fibers*	*2*	*Cereals*	*1*		
Omega 3	*1*			*Fish*	*1*	*Cereals*	*8*	*Fruits and vegetables*	*7*	*Chocolate*	*4*		
				Protein	*1*	*Chocolate*	*5*	*Milk*	*2*	*Fibers*	*14*		
				Soy	*2*	*Fibers*	*3*	*Milk and derivatives*	*3*	*Fruits and vegetables*	*11*		
				Beverage		*Fruits and vegetables*	*22*	*Legumes*	*2*	*Dried fruits*	*2*		
				Alcohol	*2*	*Dried fruits*	*3*	*Fish*	*3*	*Milk*	*5*		
				Soft drink	*1*	*Milk*	*6*	*Protein*	*3*	*Milk and derivatives*	*2*		
				Tea	*1*	*Milk and derivatives*	*5*	*Soy*	*2*	*Legumes*	*8*		
				Integration		*Legumes*	*2*	*Eggs*	*2*	*Fish*	*6*		
				Folic Acid	*1*	*Olive oil*	*2*	**Beverage**		*Protein*	*2*		
				Flavonoid	*1*	*Fish*	*12*	*Alcohol*	*7*	*Soy*	*5*		
				Omega 3	*1*	*Protein*	*2*	*Tea*	*3*	*Eggs*	*2*		
				C vitamin	*1*	*Soy*	*2*	*Soft drink*	*1*	*Yogurt*			
				E vitamin	*1*	*Yogurt*	*7*	**Integration**		**Beverage**	*13*		
						Beverage		*Monounsaturated fatty acids*	*3*	*Alcohol*	*7*		
						Alcohol	*10*	*C vitamin*	*1*	*Tea*	*3*		
						Tea	*3*	*Polynsatured fatty acid*	*2*	*Soft drink*			
						Soft drink	*1*	*E vitamin*	*3*	**Integration**	*4*		
						Integration				*Monounsaturated fatty acids*	*4*		
						Monounsaturated fatty acids	*3*			*Folic Acid*	*1*		
						Folic Acid	*9*			*Calcium - D vitamin*	*1*		
						Calcium - D vitamin	*2*			*Flavonoids*	*4*		
						Flavonoids	*6*			*Omega 3*	*4*		
						Omega 3	*4*			*E vitamin*	*6*		
						E vitamin	*11*			*C vitamin*	*3*		
						C vitamin	*6*			*Polynsatured fatty acid*	*2*		
						Omega 6	*2*			*Omega 6*	*1*		
						Polynsatured fatty acid	*3*						

Table 3. Distribution of primary studies included in meta-analyses considered, according to geographic area and type of nutritional support

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RESULTS

The literature search highlighted 189 references (figure 1). After the exclusion of 131 references, the remaining 58 were analyzed with the reading of full texts. 23 were excluded: 3 did not present the outcome of interest, the other 20 were excluded because they were less recent respect to those included in the review that presented the same outcomes. The selected articles were 35, of which 27 meta-analyses based on observational studies and 8 randomized controlled trials (RTC). A graphical summary results of meta-analyses were reported in figures 3-5.

Observational	ES	95% CI	Sig.
Alexander, eggs: 1/day vs <2/week 2016	0.88	0.81 , 0.97	0.005
Alexander, milk intake: high vs low 2016	0.91	0.83 , 0.99	0.036
Arab, green or black tea: 3 cups vs 1 cup 2009	0.79	0.72 , 0.86	0.000
Aune, high intake of whole grains vs low intake of whole grains 2016	0.87	0.72 , 1.05	0.148
Cai, carbohydrate intake high vs low 2019	1.12	0.93 , 1.35	0.233
Cai, glycemic index low vs high 2019	1.00	0.90 , 1.10	1.000
Cai, glycemic load high vs low 2019	1.00	0.89 , 1.12	1.000
Chen, C-vitamin intake: high vs low 2019	0.81	0.74 , 0.90	0.000
Chen, nuts: high consumption vs low 2017	0.82	0.73 , 0.91	0.000
Chen, penaut consumption: high vs low 2017	0.76	0.68 , 0.92	0.000
Cheng, MUFAs: high intake vs low 2016	0.86	0.74 , 1.00	0.050
Cheng, Vitamin E 2019	0.83	0.73 , 0.94	0.004
Kim, meat: high vs low intake 2019	1.18	1.09 , 1.28	0.000
Kim, red meat: high vs high intake 2019	1.11	1.03 , 1.20	0.007
Larsson, High intake of PUFAs vs low intake of PUFAs 2012	0.90	0.81 , 1.10	0.177
Narain, sugar-sweetened beverage: high vs low intake 2016	1.10	0.97 , 1.25	0.141
Pinpin, butter intake >14g/die 2016	1.01	0.98 , 1.03	0.433
Tang, flavonoids intake: high vs low intake 2019	0.89	0.82 , 0.97	0.007
Wu, yogurt high vs low intake 2019	1.02	0.92 , 1.13	0.706
Yan, soy: high vs low intake 2019	0.82	0.68 , 0.99	0.038
Yuan, chocolate: high intake vs low intake 2019	1.00	0.90 , 1.10	1.000
RCT			
Abdelhamind, polynsaturated fatty acid 2019	1.06	0.96 , 1.96	0.749
Bin, Vitamin E 2019	1.00	0.96 , 1.07	1.000
Bolland, calcium supplement 500 mg and D vitamin vs placebo 2011	1.20	1.00 , 1.43	0.046
Bolland, calcium: high intake from dairy products vs low 2011	0.69	0.60 , 0.81	0.000
Hooper, fatty acid diet low vs high 2019	1.00	0.89 , 1.12	1.000
Miller, folic acid supplementation vs placebo 2009	0.95	0.84 , 1.08	0.424
Tian, folic acid and other B vitamins vs no supplementation 2017	0.93	0.86 , 1.00	0.059
Tian, folic acid supplementation vs no supplementation 2017	0.79	0.68 , 0.92	0.002
Yang, folic acid supplementation vs placebo 2012	0.93	0.86 , 1.00	0.059

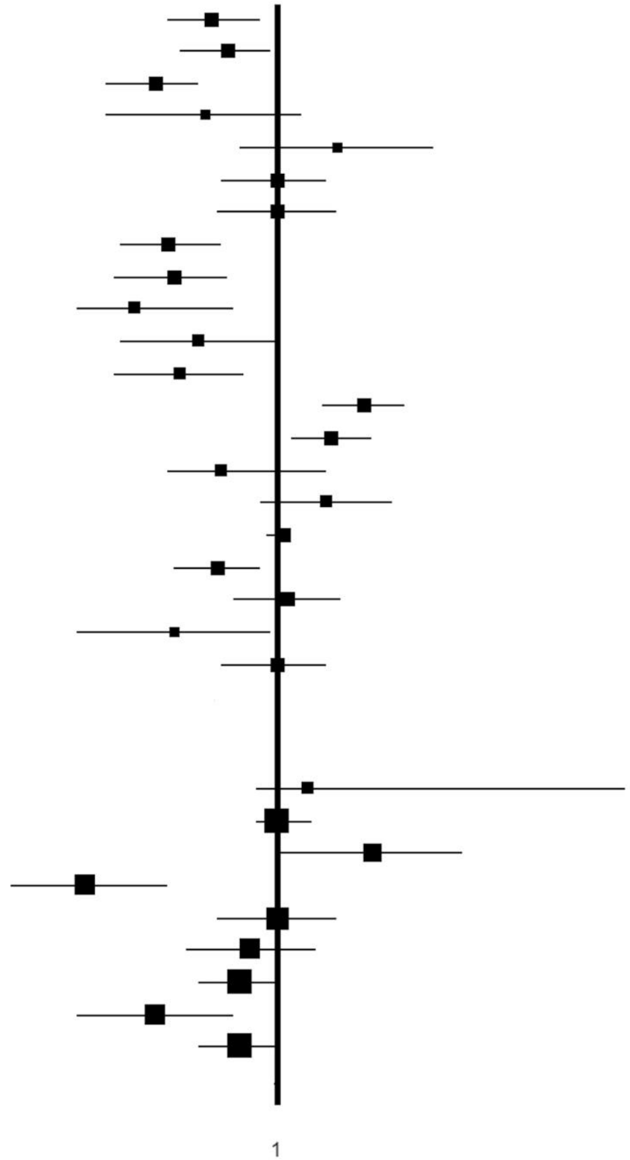

Figure 3. Summary results of effects size for any type of stroke events, based on study design of selected primary studies for each meta-analysis

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Observational	ES	95% CI	Sig.
Alexander, milk intake: high vs low 2016	0.93	0.81 , 1.06	0.290
Aune, high tree nuts consumption vs low tree nuts consumption 2016	0.93	0.77 , 1.13	0.458
Chen, C-vitamin intake: high vs low 2019	0.77	0.64 , 0.92	0.005
Cheng, MUFAs: high intake vs low 2016	0.92	0.79 , 1.08	0.296
Larrson, Heavy drinkers vs no drinkers 2016	1.13	0.95 , 1.19	0.033
Larrson, light-moderate drinkers vs never drinkers 2016	0.87	0.82 , 0.91	0.000
Larsson, High intake of PUFAs vs low intake of PUFAs 2012	0.82	0.71 , 0.94	0.006
Larsson, occasional drinkers vs light-moderate drinking 2016	0.98	0.94 , 1.04	0.433
Narain, sugar-sweetened beverage: high vs low intake 2016	1.01	0.74 , 1.37	0.950
RCT			
Abdelhamid, alpha linoleic acid 2019	1.20	0.85 , 1.69	0.298
Abdelhamid, long chain omega-3 2019	1.15	0.66 , 2.01	0.623
Bin, Vitamin E 2019	1.01	0.94 , 1.09	0.792

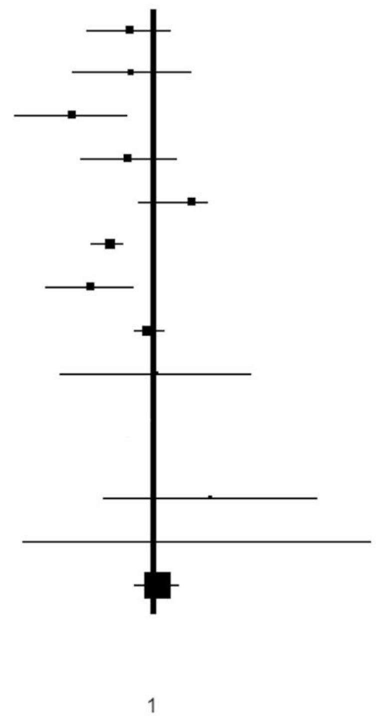

Figure 4. Summary results of effects size for ischemic of stroke events, based on study design of selected primary studies for each meta-analysis

Observational	ES	95% CI	Sig.
Alexander, cheese: high vs low intake 2016	0.87	0.77 , 0.99	0.030
Alexander, milk intake: high vs low 2016	0.93	0.69 , 1.25	0.632
Chen, C-vitamin intake: high vs low 2019	1.07	0.38 , 3.00	0.898
Cheng, MUFAs: high intake vs low 2016	0.68	0.49 , 0.96	0.025
Larsson, High intake of PUFAs vs low intake of PUFAs 2012	0.80	0.55 , 1.15	0.236
Narain, sugar-sweetened beverage: high vs low intake 2016	0.87	0.68 , 1.12	0.274
RCT			
Abdelhamid, alpha linoleic acid 2019	1.09	0.89 , 1.33	0.400
Abdelhamid, long chain omega-3 2019	1.06	0.96 , 1.96	0.749
Bin, Vitamin E 2019	1.12	0.94 , 1.33	0.201

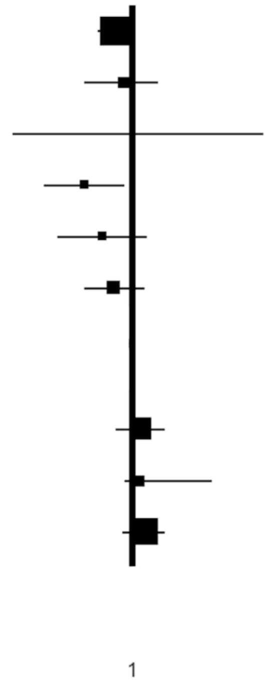

Figure 5. Summary results of effects size for hemorrhagic of stroke events, based on study design of selected primary studies for each meta-analysis

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Dairy products

Four meta-analyses specifically investigated the use of milk and dairy products. In the work of Mullie et al. [9] it is evident that the consumption of 200 ml of milk does not lead to an increased risk of stroke, while Alexander et al. [5] show that risk reduction appears to border statistical significance. Surprisingly, however, the consumption of cheese seems to reduce stroke risk (Table 1). The latter author has also performed a dose-response analysis which suggests that in total the intake of dairy products is protective against stroke; specifically, the daily consumption of cheese with a range from 0.5 to 1.5 servings; in particular, an intake of calcium from dairy products of 100-300 mg/dl or above 300 mg/dl also helps to protect (Table 2). On the other hand, a single meta-analysis investigated the correlation between risk of developing stroke and consumption of butter [10] and did not show a statistically significant increase in risk (Table 1). The paper by Wu et al concerned specifically yogurt consumption, but its outcome was not statistically significant, RR= 1.02 (0.92-1.13). This evidence was similar also in the dose-response analysis: for quantities below 200 gr / day, RR= 1.06 (0.98-1.15), for quantities above 200 gr / day, RR= 0.92 (0.85-1.00) [31]. Instead, the more controversial use of calcium along with vitamin D versus placebo shows a RR= 1.20 (1.00-1.43) [32].

Alcohol consumption

Two meta-analyses have been identified that affect alcohol as a risk factor for stroke [8,11]. It is possible to summarize the effect of alcohol on stroke substantially as a biphasic effect: protective, if consumed within the limits of 1-2 alcoholic units but very detrimental in the case of more than 4 alcoholic units (conventionally, a drink containing 8 mg of ethanol is identified as an alcoholic unit). Specifically, the consumption of alcohol seems to be protective in ischemic stroke comparing to mild and moderate consumption versus non-drinkers, with a RR= 0.87 (0.81-0.92). As for the impact of alcohol on hemorrhagic stroke, the heavy drinker shows a markedly higher risk for the onset of intracerebral hemorrhage when compared to the occasional drinker: RR = 1.74 (1.45-2.09) [11]. Larsson et al [11] performed a dose-effect analysis was to confirm the above data. The consumption of 1-2 alcoholic units a day have a protective effect against ischemic stroke. On the other hand, consumption of 4 alcoholic units is associated with an increased risk of ischemic or hemorrhagic stroke [11].

Zhang's meta-analysis also shows how a moderate consumption of alcohol has a protective effect compared to heavy consumption [8].

Mono-unsaturated [MUFAs] and polyunsaturated [PUFAs] fatty acids

A meta-analysis with 10 cohort studies included [14], investigated the consumption of MUFAs; its results show that RR is at the limits of statistical significance [Table 1].

Meta-analyses of Abdelhamid [33] and Hooper [34] on RTC showed that omega 3 and omega 6 do not influence stroke risk, respectively: RR= 1.06 (0.96-1.16) and RR= 1.36 (0.45-4.11). Larsson et al. [15] investigated the consumption of PUFAs, also on cohort studies, finding these molecules to be protective of ischemic stroke [Table 1]. On the contrary, Abdelhaimid's meta-analysis [35] on RTC showed a not significant PUFA effect on stroke risk: RR= 0.91 (0.58-1.44).

Saturated fatty acids

Muto et al [36] investigated the effect of a diet rich in saturated fatty acids. They showed that with regard to ischemic stroke, the overall HR was 0.89 (0.82-0.96), while it was 0.68 (0.47-0.96) for hemorrhagic stroke.

Hazelnuts

Chen [19] investigated the consumption of nuts and the incidence of stroke. The consumption of hazelnuts appears to be protective against stroke (Table 1). There are, however, some differences regarding the consumption of different type of hazelnuts (Table 1).

In the dose-effect study, Chen shows how a weekly consumption of up to 5 portions could to reduce mortality [17] (table 2).

Black and green tea

A meta-analysis by Arab et al. [24] investigated the consumption of green and black tea as a protective factor in the onset of stroke. The results, shown in table 1, appear to be rather encouraging, favoring a reduction in the risk of stroke.

Sugary drinks

Narain et al. [38] have studied the consumption of sugary drinks, determining how a high intake of such drinks, especially in women, seems to favor ischemic stroke [Table 1].

Whole Grains

One meta-analysis investigated the protective use of whole grains in the development of cardiovascular diseases and also in strokes [28]. This evidence was confirmed even after the dose-response analysis (Table 2).

Fruit and vegetables

Aune's research illustrated the benefit of consumption of fruits and vegetables against the onset of stroke (Table1). The benefit appears evident in the dose-response study, particularly for certain categories of plant-based foods, such as citrus fruits and citrus juices, for ischemic and hemorrhagic stroke, and the consumption of leafy vegetables for the onset of only ischemic stroke [17] (Table 2).

Vitamin B complex

A recent meta-analysis shows that folic acid can reduce stroke risk with a RR= 0.79 (0.68-0.92); while, the combined intake of folic acid + other B-complex vitamins does not appear to be significant, with a RR= 0.91 (0.82-1.00) [25].

Carbohydrate intake

A meta-analysis analyzed the incidence of stroke with respect to the total consumption of carbohydrates and respect to their glycemic index and glycemic load [39]. The risk of stroke incidence was significant in foods with a higher glycemic load: RR= 1.19 (1.05-1.36). No statistical significance was found for the consumption of the glycemic carbohydrate index (RR= 1.1, 0.99-1.21) and for global carbohydrate consumption (RR= 1.12, 0.93-1.25) [35].

Soy

A meta-analysis investigated soy consumption and analyzed 11 observational studies, including 4 case-controls and 7 cohort studies [40]. The categories with high soy consumption were compared to those with low soy consumption. In the cumulative analysis soy consumption reduced the risk of stroke significantly (RR= 0.82, 0.68-0.99) [40].

Fibers

The meta-analysis by Zhang et al. on fiber consumption highlighted how high fiber intakes are associated with a reduction in RR stroke. In particular, high fiber consumption proved to be protective in ischemic stroke (RR= 0.83, 0.74-0.93), but not in hemorrhagic stroke (RR= 0.87, 0.72-1.05). The dose-response analysis showed that the daily intake of 5 grams of fiber leads to a risk reduction (RR= 0.90, 0.82-0.99). A further increase of 10 grams shows a higher decrease of RR= 0.84 (0.75-0.94) [41].

Flavonoids

High consumption of flavonoids investigated in the meta-analysis by Tang et al, is stroke protective (RR= 0.89; 0.82-0.97). The daily increase of 100 g showed no statistically significant results (RR= 0.91; 0.77-1.08) [42].

Protein

Zhang et al [43] showed that the total protein consumption does not affect stroke risk. However, the consumption of vegetable proteins could be protective (RR= 0.90; 0.82; 0.99).

Fish

Qin's meta-analysis investigated fish consumption [44]. There is no significant relative risk in the comparison between the consumption of lean fish and fatty fish (RR=0.88; 0.74-1.04), while there is a protective effect in the consumption of large quantities of lean fish compared to the consumption of few quantities of lean fish (RR=0.81; 0.67-0.99). Xun’s meta-analysis [45] shows how a large consumption of fish has a protective effect against stroke: OR= 0.91 (0.85-0.98).

Meat

Kim et al investigated the incidence of stroke with respect to meat consumption. Red meat consumption is associated with an increase of risk (RR=1.11; 1.03-1.20). On the other hand, there is a protective effect in the consumption of white meat (RR=0.87; 0.78-0.96) [46].

Chocolate

Chocolate consumption shows a protective effect against stroke: RR= 0.84 (0.78-0.90) [47].

Vitamin C

The meta-analysis of Chen et al. concerned vitamin C intake [48]. Consumption of high doses is preventive in the development of ischemic or hemorrhagic stroke (RR= 0.81; 0.74-0.90). Similarly, the dose-response analysis verified that the incremental intake of 100 mg / day of vitamin C has a protective role in the incidence of stroke, RR= 0.82 (0.75-0.93). In particular, the intake of vitamin C would seem to be protective against ischemic stroke, RR= 0.77 (0.64-0.92), but not hemorrhagic (RR= 1.07; 0.38-3.00).

Legumes

The consumption of 100 grams per week of pulses showed RR= 1.07 (0.77-1.50), with regard to ischemic stroke and RR=1.23 (0.91; 1.66) as regards to hemorrhagic stroke [49].

Eggs

A moderate consume of eggs is associated with a potential decrease of stroke, RR= 0.88 (0.81-0.97) [50].

Olive oil

Martin-Gonzales‘s meta-analysis has highlighted that olive oil consumption has a protective effect against stroke: RR= 0.74 (0.60-0.92) [51].

Vitamin E

The results of a meta-analysis on RTC by Bin et al [52] show that the supplement of vitamin E is irrelevant on stroke onset, RR= 1.01 (0.94-1.07) [52]; on the other hand, the meta-analysis by

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Cheng et al. regarding observational studies, highlights that a supplement of vitamin E decreases stroke risk: RR= 0.83 (0.73-0.94) [53].

Geographical distribution of primary studies

As regards to geographical distribution of primary studies, respect to beverage, food, eating habits or integration, there is a strong difference among the areas considered (figure 2, table 3). It is important to underline that no studies about diet style were conducted in Canada and Australia.

Europe and USA are areas where the majority of studies were conducted: 8 studies on cereals in Europe, 5 in USA and 3 in Japan. Similar trend for fruits and vegetables: 22 studies in Europe, 14 in USA, 7 Japan and 1 in China-Korea-Singapore area.

It is important to underline that Europe and USA have also a particular interest to investigate alcohol use (figure 2, table 3); in fact, they have conducted 10 and 13 works respectively, while only 2 studies in China-Korea-Singapore region. All areas considered have studied with particular attention integrations (omega 3) (figure 2, table 3).

DISCUSSION

Our review aims to carry out an overview of meta-analyses about the impact of nutrition in the prevention of ischemic/hemorrhagic stroke. Compared to a recent review [54] we wanted to underline some aspects: first, the geographical setting of conducting individual primary studies; second, study design of primary studies (cohort o RTC) and third, methodology quality of meta-analyses. Respect to the first point, it is important to underline that all primary studies came from countries with high income levels. This evidence shows that as many countries are not represented, therefore consequent different lifestyles, ethnic groups, potentially harmful or virtuous eating habits are not reported. Moreover, different production standards, regulated by different national or international legislation, could influence the final summary of the data in evidence.

Omega 3 and 6 integrators are the most studied, both in meta-analyses of observational studies and RTC. Discrepancies emerge on the long-chain omega 3 between the meta-analysis of Larsson [15] and that of Abdelhamid [35]: probably this difference is attributable to a greater sample size in Larsson's meta-analysis and to more recent publications.

Another highly studied integrator is vitamin C (in China-Singapore-Korea, Europe and USA). Vitamin C could have a neuroprotective action due to its antioxidant activity. Murine model studies have shown that high circulating levels of vitamin C may be able to reduce the ischemic area [55]. However, a Japanese population-based study noted that vitamin C neuroprotection activity would be more effective in non-smokers than smokers, demonstrating that the overall lifestyle is responsible for cardiovascular events [56].

Flavonoids act like to vitamin C. Studies have been conducted in Europe, USA and China-Singapore-Korea area (figure 2). Flavonoids perform a neuroprotective action through a triple mechanism: reducing reactive oxygen species (ROS), reducing intracellular concentration of glutamate and inducing the production of nitric oxide (NO) by activating the enzyme NO-synthase, a powerful vasodilator [57]. However, a Japanese population-based study noted that vitamin C neuroprotection would be more effective in non-smokers than smokers [56].

The role of some vitamins in relation to cardiovascular risk has also been studied. B vitamins, in particular folic acid, cardiovascular diseases, may be linked to the improvement of endothelial function, associated with the increase of 5-methyltetrahydrofolate reductase with the reduction of the circulating homocysteine [58]. Vitamin E, instead could play a role in endothelial homeostasis in respect to local inflammation, lipid metabolism and the stability of atherosclerotic plaques [59].

Comparing the geographical areas examined, USA and Europe show particular attention to lifestyles. In fact, numerous studies have been conducted in these continents also in relation to alcohol consumption (figures 2, table 3). This data could be considered as an indicator of awareness with respect to food education policies and social habits which, however, appear to be very different between different nations, as in the case of Europe [60]. It is well known how the adoption of a healthy diet, with an adequate intake of carbohydrates, greatly reduces cardiovascular risk and obesity [61].

Regarding tea consumption there are primary studies (figures 2, table 3). Tea as a drink originated in Asia and consumption is widespread worldwide. Among the other substances contained in tea leaves, the beneficial effects are attributed mostly to Camelia Sinenis, a plant rich in catechins – molecules with a positive effect on endothelial function [62]. The benefit of this product in the meta-analysis of Arab et al has been shown for both Asians and Non-Asians [24].

There are many studies on cereals in a great part of the areas considered (figure 2). It is important to underline that cereals have not shown a potential benefit on stroke onset [28]; on the contrary, the consumption of fresh fruit, nuts and legumes entails a potential risk reduction [19,28,40,49].

Their consumption is encouraged by all the most recent guidelines on cardiovascular prevention [54,63,64] even though there are notable differences between geographical areas and social context [18,63]. As pointed out by Lake et al. climate change could also affect the accentuation of inequalities in access to food and healthy food particularly in developing countries [65,66].

The results of the studies regarding red meat are controversial. Excessive consumption of red meat and specially processed meat, studied in only two geographical areas (Europe and USA), show an increase in risk; while moderate consumption of red meat does not lead to an alteration of the lipidic structure or a significant pressure rise [67]; moreover, cardiovascular risk could be mitigated by the adequate consumption of fruit and vegetables [68].

Finally, it is important to underline that same widespread types of cancer, such as i.e. colorectal and breast cancer [69-71], and cardiovascular diseases have in common many risk factors.

CONCLUSIONS

Most physicians and health professionals underestimate the importance of food and lifestyles, smoking, consumption of alcohol, daily exercise as stroke risk factor. It is very important to underline nutrition in stroke prevention.

This review reveals that choosing foods with a more favorable nutritional profile may help reduce the risk of cardiovascular diseases and stroke in particular. These indications can be specifically addressed to those classes of the population with an increased risk of stroke, using a "tailored"

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preventive medicine for individuals based on genetic predisposition, presence of other risk factors or predisposing lifestyles.

Although far from identifying a "superfood" with nutraceutical properties that can guarantee absolute well-being or zero risk, it is clear that the choice of a balanced can reduce the risk of stroke, a disease with high social costs.

Ludwig Feuerbach in 1850 wrote *"You are what you eat"*. The research carried out so far on nutrition confirms this brilliant statement. Governments should back public health policies and promote healthy lifestyles.

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Supplementary Materials

Table S1: Evaluation of selected meta-analysis according with AMSTAR-2 Scale.

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Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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