nature communications

Impact factor: 16.6 (2022)

https://doi.org/10.1038/s41467-023-43444-3

Article

Dietary circadian rhythms and cardiovascular disease risk in the prospective NutriNet-Santé cohort

Received: 18 April 2023

Accepted: 9 November 2023

Published online: 14 December 2023

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Introduction

- **Diet** is a major risk factor for cardiovascular disease and contributes to **7.94** million CVD-related deaths annually.
- The accelerated modern lifestyle linked with the perception of lacking time in Western societies, and the current surge in fasting practices promoting meal skipping, has led to mistimed nutritional behaviours, such as late-night eating and breakfast skipping.
- The daily eating/fasting cycle is a dominant synchroniser of circadian rhythms in peripheral organs including mainly the liver, but also the heart, kidney and pancreas, and has an influence on cardiometabolic functions including the regulation of blood pressure.

Introduction…

- Data from observational and interventional studies indicate that breakfast consumption is an important habit for cardiometabolic health while its omission has been associated with overweight and obesity, risk of CVD and diabetes mellitus.

- Similarly, late-night eating has been linked in prospective studies to cardiovascular risk factors such as arterial stiffness, obesity, dyslipidaemia, metabolic syndrome (in women only) and to a higher risk of coronary heart disease in one prospective study.

Introduction…

- The main objective of the present study is to explore the associations of time of first and last meal of the day, number of eating occasions and nighttime fasting duration, with the risk of CVD, in the prospective NutriNet-Santé cohort.

Methods

❖The NutriNet-Santé cohort

✓The NutriNet-Santé cohort study was launched in France in 2009 and aimed to better understand the relationship between nutrition and health. This is an ongoing web-based cohort study that targets volunteers aged 18 or older recruited through various multimedia channels (https://etude-nutrinet-sante.fr/).

✓Participants are invited to complete a set of questionnaires including data on socio-demographics and lifestyle, physical activity (through a validated 7-day assessment, the International Physical Activity questionnaire - short form [IPAQ]), anthropometrics, health status and diet (details below).

Methods…

❖Dietary assessment

- ✓Diet was assessed from baseline with bi-annual series of 3 random records of 24 h food intake (including information on a non-working day).
- ✓Participants had to report all foods and beverages consumed and also when during the day they consumed them.
- ✓Baseline dietary intakes were assessed by averaging the consumption over the food records available from the two first years of follow-up, considered as the habitual dietary behaviours.
- ✓We estimated mean daily intakes of energy, alcohol, macro and micronutrients for this period. We used basal metabolic rate and the Goldberg cut-off method to identify and exclude energy under reporters.

Methods…

- To estimate the time of first and last meal of the day and the number of eating occasions, we computed an average of the food records available from the first two years of follow-up and we included only participants with at least 3 dietary records.
- An eating occasion was defined as the intake of any food or beverage of at least 1 kcal, thus excluding water drinking but including all other eating episodes.
- We also decided to exclude participants reporting the consumption of a first meal after 3PM or a last meal before 3PM since they corresponded to very disrupted circadian behaviours (e.g. night shift workers).
- Finally, we calculated nighttime fasting duration as follows: 24 h minus the time elapsed between the first and the last meal of the day.

Methods…

❑ Ascertainment of cardiovascular disease events

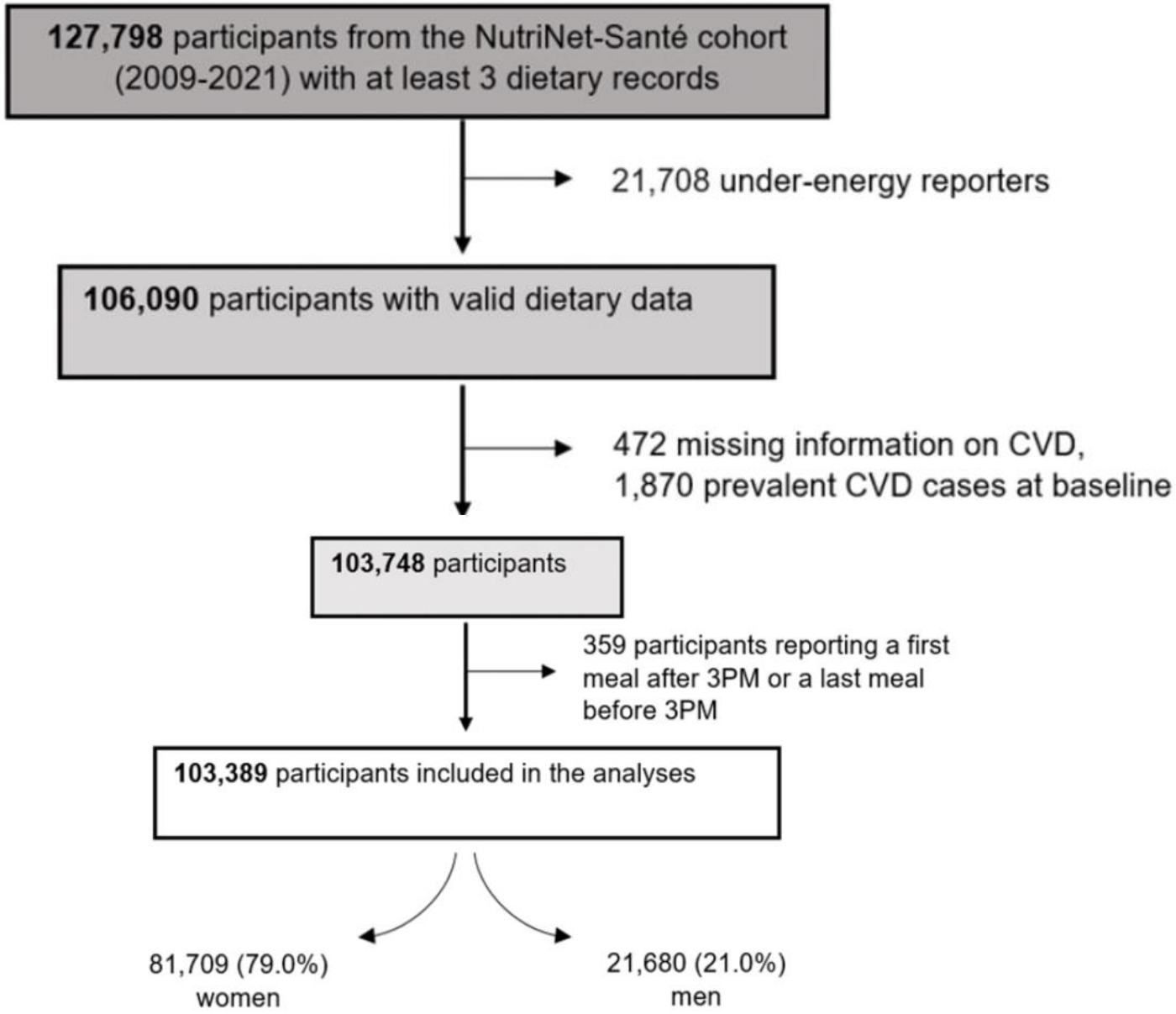
- ✓Major health events, including CVD, were self-reported by the participants through a health questionnaire sent every 6 months, or through a permanently available platform dedicated to health events collection on the NutriNet-Santé website.
- ✓Physicians from the research team reviewed the medical records and validated health events and in case of any doubt contacted the physician of the participant. Similarly, participants' families or doctors were contacted if there was no response in the website for more than a year.
- ✓Finally, deaths were assessed with the linkage to the French national cause-specific mortality registry (CépiDC).
- ✓We classified stroke and transient ischemic attack as **cerebrovascular diseases** and myocardial infraction, angina pectoris, acute coronary syndrome and angioplasty as **coronary heart diseases.**

Methods…

❑Statistical analyses

- ❖ As of October 5th 2021st, 103,389 participants without prevalent CVD at baseline were included in the present analyses.
- ❖ Time of first and last meal of the day and number of eating occasions were considered as continuous (per hour increase and per meal increase, respectively) and categorical variables, as an approximation of the tertiles in the general population.
- ❖ We built cause-specific Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations of meal timing and number of eating occasions with risk of developing overall CVD, cerebrovascular diseases and coronary heart disease.

Methods…


127,798 participants from the NutriNet-Santé cohort (2009-2021) with at least 3 dietary records
21,708 under-energy reporters
106,090 participants with valid dietary data
472 missing information on CVD,
1,870 prevalent CVD cases at baseline
103,748 participants
359 participants reporting a first meal after 3PM or a last meal before 3PM
103,389 participants included in the analyses
81,709 (79.0%) women
21,680 (21.0%) men

Results

❖Overall, younger participants, students or unemployed, single, without a family history of CVD, current regular smokers, with higher physical activity levels, higher educational levels and lower monthly incomes tended to have later first and last meals.

Results

Table 1 | Baseline characteristics of the included participants from the NutriNet-Santé cohort, 2009–2021, *N* = 103,389

	All participants	Time of first meal			Time of last meal		
		Before 8AM	8AM to 9AM	After 9AM	Before 8PM	8PM to 9PM	After 9PM
	N = 103,389	*N* = 46,306	*N* = 36,981	*N* = 20,102	*N* = 34,723	*N* = 45,610	*N* = 23,056
	N (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)
Age at baseline	42.6 (14.5)	46.5 (13.1)	42.5 (14.8)	33.9 (13.3)	45.7 (14.7)	41.7 (14.1)	39.8 (14.1)
Sex							
Women	81,709 (79.0)	35,699 (77.1)	29,817 (80.6)	16,193 (80.6)	27,284 (78.6)	36,826 (80.7)	17,599 (76.3)
Men	21,680 (21.0)	10,607 (22.9)	7164 (19.4)	3909 (19.4)	7439 (21.4)	8784 (19.3)	5457 (23.7)
BMI (kg/m^2)	23.8 (4.5)	23.9 (4.43)	23.7 (4.42)	23.5 (4.74)	24.0 (4.49)	23.6 (4.41)	23.7 (4.62)
Family history of CVD							
No	70,649 (69.4)	30,447 (65.8)	25,804 (69.8)	15,967 (79.4)	23,272 (67.0)	32,277 (70.8)	16,669 (72.3)
Yes	31,171 (30.6)	15,859 (34.2)	11,177 (30.2)	4135 (20.6)	11,451 (33.0)	13,333 (29.2)	6387 (27.7)
Smoking status[a]							
Regular current	12,442 (12.0)	4621 (9.99)	4184 (11.3)	3637 (18.1)	2942 (8.48)	5144 (11.3)	4356 (18.9)
Occasional current	5425 (5.25)	1772 (3.83)	2069 (5.60)	1584 (7.89)	1358 (3.91)	2476 (5.43)	1591 (6.91)
Former	33,563 (32.5)	16,833 (36.4)	11,941 (32.3)	4789 (23.9)	11,856 (34.2)	14,859 (32.6)	6848 (29.7)
Never	51,866 (50.2)	23,040 (49.8)	18,760 (50.8)	10,066 (50.1)	18,537 (53.4)	23,090 (50.7)	10,239 (44.5)
Packs per year[b]	5.30 (11.3)	6.01 (12.1)	5.04 (10.9)	4.18 (9.84)	5.20 (11.6)	4.92 (10.5)	6.20 (12.3)
Physical activity[c]							
Low	29,164 (32.7)	14,762 (31.9)	9876 (26.7)	4526 (22.5)	10,470 (30.2)	12,341 (27.1)	6353 (27.6)
Moderate	21,674 (24.3)	22,637 (48.9)	19,224 (52.0)	10,690 (53.2)	17,155 (49.4)	23,573 (51.7)	11,823 (51.3)
High	38,334 (43.0)	8907 (19.2)	7881 (21.3)	4886 (24.3)	7098 (20.4)	9696 (21.3)	4880 (21.2)

Results…

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	N (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)
Daily alcohol intake[d]							
Non-consumers	32,102 (31.0)	13,837 (29.9)	10,624 (28.7)	7641 (38.0)	12,432 (35.8)	12,975 (28.4)	6695 (29.0)
Low consumption	26,897 (26.0)	12,670 (27.4)	9840 (26.6)	4387 (21.8)	9419 (27.1)	12,155 (26.6)	5323 (23.1)
Medium consumption	26,241 (25.4)	11,997 (25.9)	9812 (26.5)	4432 (22.0)	8023 (23.1)	12,311 (27.0)	5907 (25.6)
High consumption	12,658 (12.2)	5545 (12.0)	4718 (12.8)	2395 (11.9)	3522 (10.1)	5811 (12.7)	3325 (14.4)
Very high consumption	5491 (5.31)	2257 (4.87)	1987 (5.37)	1247 (6.20)	1327 (3.82)	2358 (5.17)	1806 (7.83)
Episodes of binge drinking[e]							
None	92,700 (89.7)	42,301 (91.4)	32,959 (89.1)	17,440 (86.8)	32,183 (92.7)	40,587 (89.0)	19,930 (86.5)
One	7888 (7.6)	2971 (6.4)	2985 (8.1)	1932 (9.6)	1943 (5.6)	3722 (8.2)	2223 (9.6)
More than one	2788 (2.7)	1029 (2.2)	1032 (2.8)	727 (3.6)	594 (1.7)	1296 (2.8)	898 (3.9)
Daily energy intake (kcal)	1847 (451)	1856 (448)	1857 (441)	1810 (475)	1789 (434)	1852 (437)	1926 (490)
Higher education							
No	17,868 (17.3)	9476 (20.5)	5851 (15.8)	2541 (12.7)	8042 (23.2)	6669 (14.6)	3157 (13.7)
Yes, <2 y after high-school	16,318 (15.8)	7166 (15.5)	5451 (14.7)	3701 (18.4)	6054 (17.4)	6918 (15.2)	3346 (14.5)
Yes, ≥2 y after high-school	69,133 (66.9)	29,635 (64.0)	25,659 (69.4)	13,839 (68.9)	20,604 (59.4)	31,992 (70.2)	16,537 (71.8)

Results…

Table 1 | Baseline characteristics of the included participants from the NutriNet-Santé cohort, 2009–2021, *N* = 103,389

	All participants	Time of first meal			Time of last meal		
		Before 8AM	8AM to 9AM	After 9AM	Before 8PM	8PM to 9PM	After 9PM
	N = 103,389	*N* = 46,306	*N* = 36,981	*N* = 20,102	*N* = 34,723	*N* = 45,610	*N* = 23,056
	N (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)
Income per unit of consumption							
Less than 900€	11,381 (11.0)	3550 (7.67)	3829 (10.4)	4002 (19.9)	3619 (10.4)	4680 (10.3)	3082 (13.4)
900–1200€	6761 (6.55)	3060 (6.62)	2342 (6.34)	1359 (6.77)	2478 (7.14)	2870 (6.30)	1413 (6.14)
1200€ – 1800€	25,387 (24.6)	11,547 (25.0)	9030 (24.4)	4810 (24.0)	8975 (25.9)	10,918 (24.0)	5494 (23.9)
1800€ – 2300€	14,721 (14.3)	6929 (15.0)	5228 (14.1)	2564 (12.8)	4953 (14.3)	6495 (14.3)	3273 (14.2)
2300€ – 3700€	23,033 (22.3)	11,247 (24.3)	8573 (23.2)	3213 (16.0)	7459 (21.5)	10,621 (23.3)	4953 (21.5)
More than 3700€	9761 (9.45)	4903 (10.6)	3654 (9.89)	1204 (6.00)	2789 (8.04)	4716 (10.4)	2256 (9.80)
Don't wish to answer	12,236 (11.8)	5022 (10.9)	4294 (11.6)	2920 (14.5)	4412 (12.7)	5265 (11.6)	2559 (11.1)
Profession							
Unemployed	11,818 (11.5)	4128 (8.94)	4417 (12.0)	3273 (16.4)	4018 (11.6)	4968 (10.9)	2832 (12.3)
Student	6821 (6.62)	1320 (2.86)	2231 (6.06)	3270 (16.3)	1877 (5.43)	3085 (6.79)	1859 (8.09)
Self-employed/farmer	2649 (2.57)	1329 (2.88)	871 (2.36)	449 (2.24)	785 (2.27)	1221 (2.69)	643 (2.80)
Employed	65,647 (63.7)	31,096 (67.4)	22,877 (62.1)	11,674 (58.3)	20,313 (58.7)	30,123 (66.3)	15,211 (66.2)
Retired	16,077 (15.6)	8285 (17.9)	6447 (17.5)	1345 (6.72)	7598 (22.0)	6055 (13.3)	2424 (10.6)
Marital status							
Single	17,516 (17.0)	5540 (12.0)	5876 (15.9)	6100 (30.4)	4981 (14.4)	7348 (16.1)	5187 (22.5)
Married or in couple	74,888 (72.6)	35,083 (76.0)	27,276 (74.0)	12,529 (62.5)	25,647 (74.1)	33,743 (74.2)	15,498 (67.4)
Divorced, separated or widower	10,723 (10.4)	5566 (12.1)	3730 (10.1)	1427 (7.12)	3995 (11.5)	4410 (9.69)	2318 (10.1)

Results…

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		Before 8AM	8AM to 9AM	After 9AM	Before 8PM	8PM to 9PM	After 9PM
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	N (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)
Number of used medications at baseline	1.26 (1.83)	1.20 (1.77)	1.31 (1.85)	1.31 (1.91)	1.28 (1.83)	1.22 (1.75)	1.32 (1.97)
Time of first meal (AM)	8:14 (1.1)	7:22 (0.48)	8:24 (1.63)	9:57 (1.02)	7:56 (1.01)	8:14 (1.02)	8:42 (1.32)
Time of last meal (PM)	8:24 (1.1)	8:06 (1.02)	8:14 (1.00)	8:48 (1.28)	7:18 (0.74)	8:24 (0.28)	9:48 (0.90)
Eating jet lag							
Advance	5667 (5.6)	2108 (4.7)	1669 (4.6)	1890 (9.7)	2308 (6.8)	1311 (2.9)	2048 (9.1)
Maintenance	69,867 (69.3)	33,421 (74.3)	25,244 (69.5)	11,202 (57.4)	24,171 (71.3)	32,299 (72.4)	13,397 (59.9)
Delay	25,322 (25.1)	9469 (21)	9420 (26)	6433 (32.9)	7417 (21.9)	10,972 (24.6)	6933 (31.0)
Nighttime fasting hours	11.9 (1.4)	11.2 (1.09)	12.0 (1.01)	13.2 (1.51)	12.6 (1.26)	11.8 (1.02)	10.9 (1.46)
Number of eating occasions/day	4.89 (1.7)	5.00 (1.78)	4.89 (1.63)	4.63 (1.71)	4.41 (1.40)	4.82 (1.55)	5.73 (2.14)
Bedtime[f]	23:42 (0.94)	23:30 (0.84)	23:54 (0.86)	24:12 (1.15)	23:24 (0.88)	23:48 (0.84)	24:12 (1.05)
Sleep duration (h)	6.93 (1.59)	6.75 (1.56)	7.03 (1.60)	7.24 (1.59)	6.94 (1.65)	6.95 (1.57)	6.86 (1.53)

Results…

❑Association of meal timing and number of eating occasions with CVD risk

- ✓During a median follow-up time of 7.2 years (1st quartile [Q1] – 3rd quartile [Q3], 3.1–10.1) and 699,547 person-years, 2036 incident cases of CVD were ascertained.
- ✓There were 988 cases of cerebrovascular diseases (253 cases of stroke and 765 of transient ischemic attack) and 1071 cases of coronary heart diseases (162 cases of myocardial infraction, 428 of angioplasty, 89 of acute coronary syndrome and 428 of angina pectoris).

Results…

We observed that each additional hour in delaying the time of first meal of the day was associated with a higher risk of overall CVD (HR = 1.06, 95% CI 1.01–1.12, P-value = 0.02).

Table 2 | Association of meal timing and number of eating occasions with risk of cardiovascular diseases in the NutriNet-santé cohort, 2009-2021, *N* = 103,389

	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Overall cardiovascular diseases			
Time of first meal (1 h incr.)	2036/101,353	1.06 (1.01–1.12)	0.02
Before 8AM	1040/45,266	Ref.	0.06
Between 8 and 9AM	764/36,217	1.07 (0.97–1.17)	
After 9AM	232/19,870	1.14 (0.98–1.32)	
Time of last meal (1 h incr.)	2036/101,353	1.02 (0.98–1.07)	0.4
Before 8PM	786/33,937	Ref.	0.06
Between 8 and 9PM	844/44,766	1.08 (0.97–1.19)	
After 9PM	406/22,650	1.13 (0.99–1.29)	
Number of eating occasions (1 occasion incr.)	2036/101,353	0.99 (0.96–1.02)	0.5

Results…

Each additional hour in delaying the time of last meal was associated with an 8% increased risk of cerebrovascular disease (HR = 1.08, 95% CI 1.01–1.15, P-value = 0.02): more specifically, compared to a last meal before 8PM, a last meal after 9PM was associated with a 28% higher risk of cerebrovascular disease (HR = 1.28, 95% CI 1.05–1.55, P-trend < 0.01).

Table 2 | Association of meal timing and number of eating occasions with risk of cardiovascular diseases in the NutriNet-santé cohort, 2009-2021, *N* = 103,389

	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Cerebrovascular diseases[c]			
Time of first meal (1 h incr.)	988/102,401	1.06 (0.98–1.14)	0.1
Before 8AM	508/45,798	Ref	0.1
Between 8 and 9AM	361/36,620	1.02 (0.89–1.17)	
After 9AM	119/19,983	1.23 (0.99–1.52)	
Time of last meal (1 h incr.)	988/102,401	1.08 (1.01–1.15)	0.02
Before 8PM	363/34,360	Ref.	<0.01
Between 8 and 9PM	426/45,184	1.19 (1.03–1.37)	
After 9PM	199/22,857	1.28 (1.05–1.55)	
Number of eating occasions (1 occasion incr.)	988/102,401	0.97 (0.93–1.01)	0.1

Results…

Table 2 | Association of meal timing and number of eating occasions with risk of cardiovascular diseases in the NutriNet-santé cohort, 2009-2021, *N* = 103,389

	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Coronary heart diseases[d]			
Time of first meal (1 h incr.)	1071/102,318	1.05 (0.98–1.13)	0.1
Before 8AM	550/45,756	Ref.	0.4
Between 8 and 9AM	406/36,575	1.09 (0.96–1.24)	
After 9AM	115/19,987	1.04 (0.84–1.29)	
Time of last meal (1 h incr.)	1071/102,318	0.97 (0.92–1.05)	0.4
Before 8PM	432/34,291	Ref.	0.9
Between 8 and 9PM	429/45,181	0.99 (0.86–1.13)	
After 9PM	210/22,846	1.00 (0.83–1.20)	
Number of eating occasions (1 occasion incr.)	1071/102,318	1.01 (0.97–1.05)	0.6

Results…

Each additional hour of nighttime fasting was associated with a 7% lower risk of cerebrovascular disease (HR = 0.93, 95% CI, 0.87–0.99, P-value = 0.02), but not with risk of overall CVD or coronary heart disease.

Table 3 | Association between daily nighttime fasting duration and risk of cardiovascular diseases in the NutriNet-Santé cohort, 2009–2021, *N* = 103,389

	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Overall cardiovascular diseases			
Continuous (1 h incr.)	2036/101,353	0.98 (0.94–1.02)	0.4
12 h or less	1207/56,813	Ref.	0.6
12 h to 13 h	558/28,380	0.91 (0.82–1.02)	
More than 13 h	271/16160	0.98 (0.84–1.14)	
Cerebrovascular diseases[c]			
Continuous (1 h incr.)	988/102,401	0.93 (0.87–0.99)	0.02
12 h or less	613/57,407	Ref.	0.02
12 h to 13h	254/28,684	0.78 (0.66–0.91)	
More than 13 h	121/16,310	0.80 (0.63–1.01)	
Coronary heart diseases[d]			
Continuous (1 h incr.)	1071/102,318	1.03 (0.96–1.09)	0.4
12 h or less	613/57,407	Ref.	0.2
12 h to 13 h	307/28,631	1.05 (0.90–1.22)	
More than 13 h	151/16,280	1.16 (0.94–1.44)	

Results…

❑Differences by sex

- The results showed a statistically significant interaction between sex and time of last meal of the day for the associations with **overall CVD (p-value = 0.01)** and **coronary heart disease risk (p-value = 0.004).**
- **The results suggest stronger associations in <u>women than in men</u>.**
- Specifically, the results show that **later times of first and last meals** were significantly associated with a **higher risk of overall CVD and cerebrovascular disease for <u>women</u>** but not for men (Table 4).

Results…

Table 4 | Association of meal timing, number of eating occasions and nighttime fasting duration with risk of cardiovascular disease by sex in the NutriNet-santé cohort, 2009-2021, *N* = 103,389

	Women			Men		
	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]	*N* cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Overall cardiovascular diseases						
Time of first meal (1 h incr.)	1106/80,603	1.06 (0.99–1.14)	0.08	930/20,750	1.06 (0.99–1.15)	0.09
Before 8AM	538/35,161	Ref	0.05	502/10,105	Ref.	0.6
Between 8 and 9AM	414/29,403	1.04 (0.91–1.19)		350/6814	1.09 (0.95–1.26)	
After 9AM	154/16,039	1.24 (1.02–1.51)		78/3831	0.98 (0.76–1.25)	
Time of last meal (1 h incr.)	1106/80,603	1.07 (1.00–1.13)	0.05	930/20,750	0.97 (0.91–1.04)	0.4
Before 8PM	387/16,039	Ref.	0.01	399/7040	Ref.	1.0
Between 8 and 9PM	479/36,347	1.12 (0.97–1.29)		365/8419	1.04 (0.89–1.20)	
After 9PM	240/17,359	1.26 (1.05–1.51)		166/5291	0.99 (0.80–1.21)	
Number of eating occasions (1 occasion incr.)	1106/80,603	0.99 (0.95 –1.03)	0.6	930/20,750	0.99 (0.95–1.03)	0.7
Nighttime fasting duration[c] (1 h incr.)	1106/80,603	0.94 (0.88–1.00)	0.05	930/20,750	1.03 (0.96–1.09)	0.4

Results…

Table 4 | Association of meal timing, number of eating occasions and nighttime fasting duration with risk of cardiovascular disease by sex in the NutriNet-santé cohort, 2009-2021, *N* = 103,389

	Women			Men		
	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]	*N* cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Cerebrovascular diseases[d]						
Time of first meal (1 h incr.)	625/81,084	1.10 (1.01–1.21)	0.03	363/21,680	0.98 (0.87–1.11)	0.8
Before 8AM	299/35,400	Ref.	0.02	209/10,398	Ref.	0.8
Between 8 and 9AM	242/29,575	1.11 (0.94–1.33)		119/7045	0.86 (0.68–1.08)	
After 9AM	84/16,109	1.35 (1.04–1.75)		35/3874	1.00 (0.69–1.46)	
Time of last meal (1 h incr.)	625/81,084	1.07 (0.98–1.16)	0.1	363/21,680	1.09 (0.99–1.21)	0.09
Before 8PM	218/27,066	Ref.	0.02	145/7294	Ref.	1.0
Between 8 and 9PM	275/36,551	1.18 (0.98–1.42)		151/8633	1.20 (0.94–1.52)	
After 9PM	132/17,467	1.31 (1.03–1.67)		67/5390	1.20 (0.87–1.67)	
Number of eating occasions (1 occasion incr.)	625/81,084	0.98 (0.93–1.04)	0.6	363/21,680	0.94 (0.88–1.01)	0.09
Nighttime fasting duration (1 h incr.)	625/81,084	0.94 (0.86 – 1.02)	0.1	363/21,680	0.91 (0.82–1.01)	0.09

Results…

Table 4 | Association of meal timing, number of eating occasions and nighttime fasting duration with risk of cardiovascular disease by sex in the NutriNet-santé cohort, 2009-2021, *N* = 103,389

	Women			Men		
	N cases/ non-cases	HR (95% CI)[a]	*p*-val[b]	*N* cases/ non-cases	HR (95% CI)[a]	*p*-val[b]
Coronary heart diseases[e]						
Time of first meal (1 h incr.)	495/81,214	0.99 (0.90–1.10)	0.9	576/21,104	1.11 (1.01–1.22)	0.03
Before 8AM	250/35,449	Ref.	1.0	300/10,307	Ref.	0.2
Between 8 and 9AM	175/29,642	0.93 (0.76–1.13)		231/6933	1.23 (1.04–1.47)	
After 9AM	70/16,123	1.06 (0.79–1.42)		45/3864	0.97 (0.70–1.35)	
Time of last meal (1 h incr.)	495/81,214	1.07 (0.97–1.18)	0.2	576/21,104	0.91 (0.84–0.99)	0.02
Before 8PM	174/27,110	Ref.	0.2	258/7181	Ref.	0.2
Between 8 and 9PM	212/36,614	1.06 (0.86–1.30)		217/8567	0.94 (0.78–1.14)	
After 9PM	109/17,490	1.18 (0.90–1.55)		101/5356	0.87 (0.67–1.12)	
Number of eating occasions (1 occasion incr.)	495/81,214	0.99 (0.93–1.05)	0.6	576/21,104	1.03 (0.98–1.08)	0.3
Nighttime fasting duration (1 h incr.)	495/81,214	0.93 (0.85–1.03)	0.2	576/21,104	1.10 (1.01–1.19)	0.02

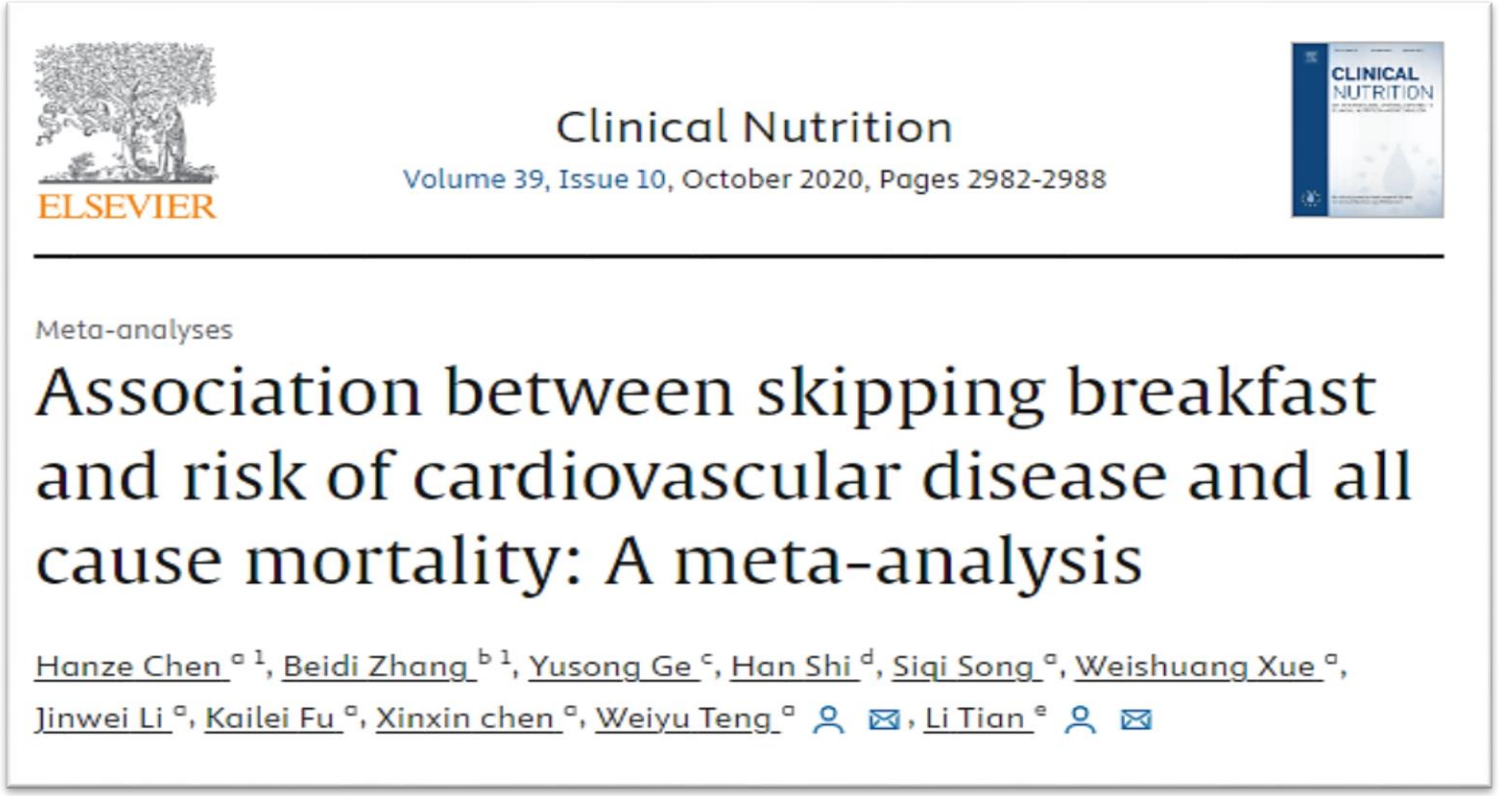
Discussion

- In this large prospective cohort study, later times of first and last meals were independently associated with a higher risk of overall CVD. These associations were stronger in women than in men.
- We observed no link between the daily number of eating occasions and the risk of overall CVD.
- In animal models, delaying the first meal of the day by 4 hours increased body weight, hepatic lipids and adipose tissue weight and delayed circadian oscillation of genes related with lipid metabolism.

Discussion…

- Mimicking late-night eating in mice has been also associated with weight gain, hepatic lipid accumulation, inflammation and microbial dysbiosis.
- Evidence from RCTs suggests that a later evening meal can lead to glucose intolerance, insulin resistance, increased cholesterol and triglyceride levels and BMI. Food intake when melatonin levels are high, during the rest phase, could lead to glucose intolerance and hyperglycaemia.
- As seen from animal and human studies, having a later first and last meal of the day could be linked to CVDs through weight gain. However, in sensitivity analyses we adjusted our primary models for weight gain during follow-up and results did not substantially change, suggesting other mechanisms could be explaining these associations.

Discussion…



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Clinical Nutrition

Volume 39, Issue 10, October 2020, Pages 2982-2988

Meta-analyses

Association between skipping breakfast and risk of cardiovascular disease and all cause mortality: A meta-analysis

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Skipping breakfast was associated with elevated risk of cardiovascular disease (relative risk 1.22 95% confidence interval 1.10–1.35) and all cause mortality (relative risk 1.25 95% confidence interval 1.11–1.40) compared with eating breakfast regularly.

Strengths of study

- The sample size, prospective design and detailed assessment of circadian dietary behaviours encompass the main strengths of this study.
- These behaviours were measured using dietary records, which are less subject to recall and misclassification bias than are dietary recalls or ad-hoc questionnaires.
- The large panel of questionnaires in the NutriNet-Santé cohort enabled us to control for a large number of well measured potential confounders, reducing the risk of confounding in the present analyses. Besides, the observational, yet prospective design has allowed us to study the long-term associations (follow-up from 2009 to 2021) between meal timing and cardiovascular diseases, which would be challenging to investigate in interventional studies, especially with hard endpoints.

Limitations of study…

- ✓Although we accounted for a large panel of confounders, given the observational nature of this study, residual confounding cannot be completely ruled out.
- ✓We had no information on exposure to light-at-night, use of recreational drugs, as well as timing of physical activity, medication or alcohol consumption which are all potential disruptors of circadian rhythms. Future studies collecting accelerometery data could be of interest to objectively account for physical activity timing and patterns.
- ✓Participants in the NutriNet-Santé cohort are volunteers and are more likely to be women, have a higher socioeconomic status and healthier behaviour patterns than the general population, somehow limiting the extrapolation of these results.
- ✓Lastly, even though meal timing showed associations with cardiovascular outcomes in our study, CVD remains amultifactorial disease, and meal timing alone could not explain the trends in CVD incidence across countries, as other demographic, lifestyle, genetic and environmental factors are involved.

Conclusion

- To conclude, in this large prospective study, later times of first and last meals were associated with a higher risk of overall CVD.
- These findings suggest that, beyond the nutritional quality of the diet itself, recommendations related to meal timing for patients and citizens may help promoting a better cardiometabolic health.

نتیجه گیری

این مطالعه NutriNet-Santé cohort در اسپانیا و فرانسه از سال ۲۰۰۹ تا ۲۰۲۱ روی ۱۰۳،۳۸۹ فرد انجام شده است.هدف این مطالعه بررسی ارتباط میان زمان خوردن صبحانه و شام با بروز بیماریهای قلبی عروقی بوده است. نتایج مطالعه نشان داد که" هرچه صبحانه و شام دیرتر مصرف شود احتمال بروز بیماریهای قلبی عروقی بالاخص در خانمها افزایش می یابد."

لذا پیشنهاد می شود صبحانه قبل از ساعت ۸ صبح و شام قبل از ساعت ۹ شب مصرف شود.

همچنین در مطالعه دیگری مشاهده شده است که **حذف صبحانه** نسبت به مصرف منظم آن باعث افزایش ۲۲ درصدی بیماریهای قلبی عروقی و افزایش ۲۵ درصدی ریسک مرگ و میر کلی می شود.

Thank you for your attention