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ORIGINAL CONTRIBUTION

The inflammatory potential of the diet is prospectively associated with subjective hearing loss

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Abstract

Purpose We investigated the association between the inflammatory potential of the diet and hearing loss in the context of aging.

Methods We studied 3435 French adults enrolled in the SU.VI.MAX 2 (2007–2009) cohort. The inflammatory potential of the diet was estimated by the Dietary Inflammatory Index (DII®) using ≥ 3 baseline 24-h dietary records. Subjective hearing loss was assessed after a mean of 12.5 ± 0.7 years by 3 individual items (ability to carry a conversation in a noisy setting, frequently asking for repetition, and need to increase the television/radio volume) and by a composite score, dichotomized for analyses. We fit sex-specific multivariable logistic regression models.

Results Compared with males, females had higher DII scores (i.e., more pro-inflammatory diet) and less subjective hearing loss. Among males, a significant positive association between DII (continuous scale) and inability to carry a conversation in a noisy setting was found (OR = 1.10; 95% CI 1.02, 1.18), while the opposite was seen among females (OR = 0.92; 95% CI 0.87, 0.98). Regarding the need to turn up the television/radio volume, a significant positive association with DII (continuous scale) was found only among males (OR = 1.09; 95% CI 1.01, 1.18). A significant association with the subjective hearing loss composite score was found among females ($OR_{Q3\ vs\ Q1}$ = 0.74; 95% CI 0.57, 0.97).

Conclusion The findings among males supported the hypothesis that a pro-inflammatory diet could increase risk of hearing loss, whereas the findings among females were unexpected. This study could provide impetus for future research in sensory disability and aging.

Trial registration www.clinicaltrials.gov # NCT00272428.

Keywords Dietary patterns · Inflammation · Dietary Inflammatory Index · Hearing loss · Aging · Public health

Introduction

Population aging is a worldwide trend that is highly correlated with the prevalence of presbycusis (or age-related sensorineural hearing loss, HL). The latter is a bilateral, irreversible condition that is manifested by a worsening ability to hear high-frequency sounds and understand speech, and that could be a precursor to dementia [1, 2]. Presbycusis results from the gradual degeneration of sensory cells (hair cells of the organ of Corti, stria vascularis, spiral ganglion neurons), accelerated by advancing age, mitochondrial DNA mutations, oxidative damage, noise exposure, ototoxic medication use, and poor diet [3–6]. Of note, the long-term adverse impact of HL on quality of life has been more salient in terms of self-perceived hearing handicap than audiometrically assessed HL [7]. Subjective

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HL displays a moderate, age-dependent correlation with objective HL measures [8, 9].

Aging and age-related chronic diseases have been associated with upregulation of pro-inflammatory mediators [tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), cyclooxygenase-2, cytokine-inducible nitric oxide synthase, C-reactive protein (CRP)], underlying low-grade chronic inflammation [10, 11]. Regarding presbycusis, cross-sectional results showed an age-dependent, inverse association of white blood cell count, IL-6 and CRP with hearing level [12, 13], whereas longitudinal results are less straightforward. For example, Nash et al. [14] reported an association between consistently high or increasing serum CRP and 10-year incident HL in those aged < 60 years; Lassale et al. [15] found a prospective association only between white blood cell count and HL in individuals with a median baseline age of 63 years; no significant results regarding the link between inflammation markers and HL risk emerged from the Nurses' Health Studies [16].

Given estimates that nearly half of all HL cases are preventable via cost-effective public health measures [17], dietary interventions are promising owing to diet's role in inflammation, blood lipids, endothelial function and blood pressure [6]. CRP concentrations were shown to be 30% and 24% lower among those in the top versus the bottom quintile of the Alternate Healthy Eating Index (AHEI) and the Alternate Mediterranean Diet Index (AMED), respectively [18]; a meta-analysis of 17 trials also reported that healthy dietary patterns [Mediterranean diet, Nordic diet, Tibetan diet, Dietary Approaches to Stop Hypertension (DASH)] were associated with reduced CRP [19]. Moreover, findings from the Nurses' Health Study II revealed that dietary patterns featuring fruit, vegetables, legumes, whole grains, nuts, poultry, and fish, with moderate alcohol intake (AMED, DASH, and AHEI-2010) were prospectively associated with lower HL risk [6]. A recent study with 734 elderly investigated the link of presbycusis with foods/beverages modeled as anti-inflammatory (fruit, vegetables, nuts, wine) or as pro-inflammatory (processed meat, sugar-rich juices, desserts, hard liquor) [20]. The researchers found that presbycusis was cross-sectionally associated with an increased intake of fruit juices and retrospectively associated with an increased intake of sugary food, high-calorie drinks, beer, and hard liquor [20]. No study has yet explored the link between the inflammatory potential of the overall diet and HL. The former is commonly estimated via a summary measure—the literature-based Dietary Inflammatory Index (DII®)—based on the evidence from 1943 peer-reviewed articles on diet and 6 of the most commonly-studied inflammatory markers [21]. This study examined the association between DII scores evaluated at midlife and subjective HL assessed later in life.

Materials and methods

We used data from the French *Supplémentation en Vitamines et Minéraux Antioxydants* trial (SU.VI.MAX, 1994–2002; $n = 12{,}741$; www.clinicaltrials.gov # NCT00272428) and its follow-up SU.VI.MAX 2 observational study (2007–2009; $n = 6850$), with males and females recruited from the general population. The former was a randomized, double-blind, placebo-controlled, primary prevention trial of the efficacy of daily antioxidant supplementation regarding risk of cancer, cardiovascular disease, and all-cause mortality. Details about the trial protocol and follow-up are published elsewhere [22]. SU.VI.MAX 2 was a cross-sectional study with 54% of the original SU.VI.MAX sample (i.e., there were no SU.VI.MAX 2 participants who had not previously been enrolled in SU.VI.MAX). All procedures were approved by the Ethics Committee for Studies with Human Participants of Paris-Cochin Hospital and the National Commission on Informatics and Liberty. Written informed consent was obtained from each participant prior to enrollment.

DII estimation

As part of the SU.VI.MAX follow-up, participants completed up to six 24-h dietary records per year with the help of a picture manual [23]. Details about the dietary data collection are available elsewhere [24]. Briefly, during the SU.VI.MAX trial (1994–2002), participants were asked to complete a 24-h dietary record every two months for a total of six such records per year. The days were assigned at random and included four weekdays and two weekend days per year. Each day of the week and all seasons had an equal chance of being covered, thus accounting not only for seasonal but also for individual variability in dietary intake. Next, nutrient intake was computed using the Phenol-Explorer database [25] and a validated food composition table [26]. For this study, mean intake of food and nutrients was calculated across all complete 24-h records (if ≥ 3 such records, in order to reduce measurement bias) collected during the first two years of follow-up (1994–1996). Hence, we excluded from the analysis 1656 individuals for whom the DII could not be calculated owing to missing dietary data or to having fewer than three 24-h dietary records. The participant inclusion flowchart is presented in Fig. 1.

DII was computed using established criteria [27]. Briefly, individual-level intake of nutrients and food was standardized to worldwide mean ± SD values, and the resulting z scores were converted to centered proportions and multiplied by a literature-derived effect score. At the individual

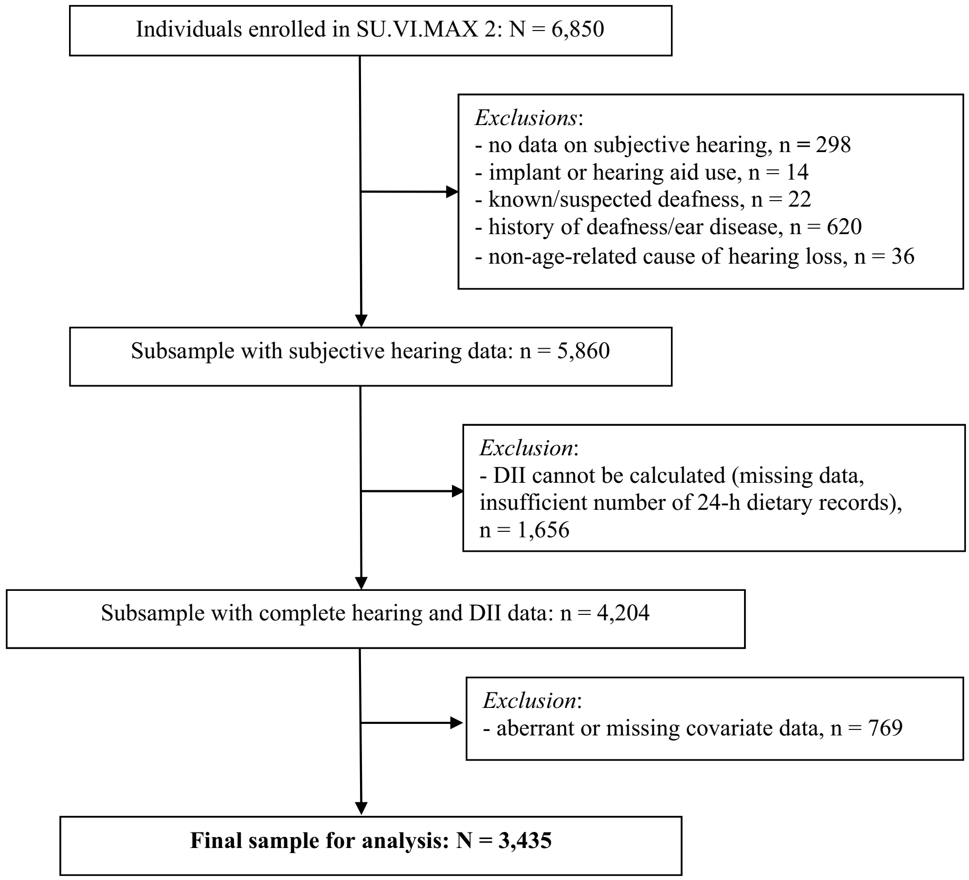

Fig. 1 Participant selection flowchart

level, all food-specific inflammatory marker values were summed to obtain the DII. Of the 45 original dietary components, the present study had data on 35: carbohydrates, fiber, protein, total/saturated/monounsaturated/polyunsaturated fatty acids, omega-3 and omega-6 fatty acids, cholesterol, niacin, thiamin, riboflavin, vitamins A, B6, B12, C, D, and E, folic acid, iron, zinc, beta-carotene, anthocyanidins, flavanols, flavonols, flavonones, flavones, isoflavones, garlic, ginger, pepper, onion, tea, and alcohol. A higher (i.e., more positive) DII corresponds to a more pro-inflammatory diet, whereas a lower (i.e., more negative) DII corresponds to a more anti-inflammatory diet [27].

Subjective hearing assessment

As part of the SU.VI.MAX 2 protocol, during the period 2007–2009, the participants underwent a comprehensive clinical examination that included an assessment of hearing level. Specifically, subjective HL was assessed with three Yes/No questions about ability to carry a conversation in a noisy setting, need to frequently ask for repetition, and need to increase the television/radio volume. A total score ranging from 0 (no problem in any area) to 3 (problems in all three areas) was calculated. Individuals with present/previous ear disease and those wearing hearing aids or other auditory devices were ineligible for the study.

Covariates

Upon enrollment in SU.VI.MAX 2, information on sex, age, education (< high school; high school diploma; Associate's degree or equivalent; undergraduate or graduate degree), occupation (homemaker, farmer/manual labor, artisan/self-employed/office worker/skilled labor, managerial staff/intellectual profession), smoking (never, former or current smoker), and leisure–time physical activity (the equivalent of fast walking) in h/week was collected via self-report questionnaires. Objective anthropometric and clinical data also were obtained. Body weight was measured with an electronic scale following standardized procedures, with barefoot participants wearing light indoor clothing; height was measured to the nearest 0.5 cm with a wall-mounted stadiometer. Body mass index (BMI) was calculated as the weight in *kg* divided by the square of height in *m*. Blood pressure was measured following a 10-min rest with a standard mercury sphygmomanometer. If systolic blood pressure was > 160 mmHg and/or diastolic blood pressure was > 100 mmHg, the assessment was repeated following a 5-min rest [28].

Statistical analysis

The sociodemographic characteristics of included and excluded (from the present analysis) SU.VI.MAX 2 participants were compared with chi-squared tests and Student *t* tests. In the final sample, descriptive analyses by sex-specific DII quartiles were performed with chi-squared tests and ANOVA. The main analysis consisted of multivariable logistic regression of the cross-time association of DII [independent variable modeled on a continuous scale (Model 1) and as sex-specific quartiles (Model 2)] with subjective HL. We hypothesized that a lower DII (i.e., less diet-associated inflammation) would be protective against HL risk. As dependent variables, we individually modeled the three Yes/No items measuring perceived (subjective) HL and the summary score (range 0–3 points), which was dichotomized for the analysis (0 = no problem; ≥ 1 = some hearing problems). All models were adjusted for supplementation group during the trial, age, education, occupation, BMI, blood pressure, physical activity, number of 24-h dietary records, dietary energy intake (without alcohol), alcohol intake, and smoking status. Unlike nonsignificant interaction by age, alcohol use, smoking and supplementation group (all $p > 0.10$), interaction by sex was statistically significant, hence separate models were fit for males and females. Finally, a sensitivity analysis was carried out, where the DII was replaced by an energy–density DII [22], which was then modeled on a continuous scale. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using SAS® (version 9.4, SAS Institute, Inc., Cary NC, USA).

Results

Participant characteristics

The sample included 3435 participants (58% females) with a mean age at the time of HL assessment of 61.7 ± 6.1 years. The mean interval between DII estimation and subjective HL assessment was 12.5 ± 0.7 years.

When compared with SU.VI.MAX 2 participants who were not included in this analysis ($n = 3415$), those who were included were somewhat younger (mean age 62.4 vs. 61.7 years), more likely to have completed primary/secondary education, to be married/cohabiting (82.1% vs. 76.8%) and to have lower blood pressure (all $p < 0.05$, data not tabulated). There were no significant differences between included and excluded participants as regards randomization group (SU.VI.MAX trial), sex, smoking status or physical activity.

The DII was normally distributed with mean values being higher among females than among males (0.84 ± 1.88 vs. 0.12 ± 1.77; $p < 0.0001$). In turn, subjective HL was more frequently reported by males than by females (50.3% vs. 38.3%; $p < 0.0001$). The sociodemographic and health status characteristics by DII quartiles are summarized in Table 1 (females) and Table 2 (males).

Association between DII and subjective HL

The results of the sex-specific multivariable logistic regression models are presented in Table 3. Among males, a significant positive association between DII (continuous scale and quartiles) and inability to carry a conversation in a noisy setting was found ($OR_{cont} = 1.10$; 95% CI 1.02–1.18; $OR_{Q4\ vs\ Q1} = 1.48$; 95% CI 1.03–2.12), while the opposite was seen among females ($OR_{cont} = 0.92$; 95% CI 0.87–0.98; $OR_{Q4\ vs\ Q1} = 0.69$; 95% CI 0.50–0.93). Regarding the need to turn up television/radio volume, a significant positive association with DII was found only among males ($OR_{cont} = 1.09$; 95% CI 1.01–1.18; $OR_{Q4\ vs\ Q1} = 1.53$; 95% CI 1.03–2.26). No association between DII and frequently asking for repetition was found in either sex. The only significant association with the dichotomized composite score of subjective HL was seen among females ($OR_{Q3\ vs\ Q1} = 0.74$; 95% CI 0.57–0.97). In the sensitivity analysis, where the DII was replaced by an energy–density DII, the main findings were largely replicated (Table 4).

Discussion

To our knowledge, this study was the first to investigate the association between the inflammatory potential of the overall diet and age-related HL. We prospectively studied a large sample of aging adults recruited from the general French population. The adjusted analysis provided some support for our hypothesis, especially among males in whom it was observed that less diet-related inflammation (i.e., lower DII scores) was associated in a protective fashion with subjective HL. This link was restricted to specific subjective HL measures, such as inability to carry a conversation in a noisy setting and need to turn up the television/radio volume. In turn, unexpected results were observed among females in whom DII and subjective HL were inversely associated. In our sample, males had lower mean DII (i.e., less pro-inflammatory diet) yet more subjective hearing impairment compared with females. There may also exist sex-specific predisposition to the type of presbycusis—sensory, neural, strial, and cochlear-conductive—along with the presbycusis manifestation (loss of word discrimination, alterations in physical characteristics of cochlear duct, etc.) [29]. In addition, total energy intake, which was taken into account in the main and sensitivity analyses, differs significantly between males and females [21]. Although sex-specific associations

Table 1 Sociodemographic, lifestyle and health status characteristics of female participants at the time of hearing level assessment, by Dietary Inflammatory Index (DII) quartiles, $N = 2010$

	Dietary Inflammatory Index (DII)				*p*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
n	502	503	502	503	
DII, mean (SD)	− 1.6 (0.8)	0.2 (0.4)	1.5 (0.4)	3.3 (0.8)	< 0.0001
Number of 24-h dietary records, mean (SD)*	9.9 (3.3)	10.2 (3.1)	10.3 (3.0)	9.9 (3.1)	0.08
Total energy intake without alcohol, kcal/day, mean (SD)*	1,992.6 (452.1)	1,886.6 (410.3)	1,753.0 (383.9)	1,550.2 (386.7)	< 0.0001
Alcohol intake, g/day, mean (SD)*	10.9 (12.7)	12.6 (14.8)	11.0 (13.0)	8.7 (11.5)	< 0.0001
Active supplementation group (1994–2002)	278 (55.4)	266 (52.9)	242 (48.2)	264 (52.5)	0.15
Age, years, mean (SD)	60.8 (6.5)	59.4 (6.5)	60.2 (6.2)	59.1 (6.1)	< 0.0001
Marital status					
Married/cohabiting	397 (79.1)	416 (82.7)	407 (81.1)	416 (82.7)	0.40
Living alone	105 (20.9)	87 (17.3)	95 (18.9)	87 (17.3)	
Educational level					
Less than high school	113 (22.5)	121 (24.0)	153 (30.5)	185 (36.8)	< 0.0001
High school diploma or equivalent	111 (22.1)	104 (20.7)	113 (22.5)	106 (21.1)	
Associate's degree or equivalent	94 (18.7)	98 (19.5)	88 (17.5)	79 (15.7)	
Undergradute or graduate degree	184 (36.7)	180 (35.8)	148 (29.5)	133 (26.4)	
Occupational category					
Homemaker, disabled, unemployed	65 (12.9)	49 (9.8)	63 (12.5)	83 (16.5)	< 0.0001
Employed, self-employed	177 (35.3)	225 (44.7)	169 (33.7)	218 (43.3)	
Retired	260 (51.8)	229 (45.5)	270 (53.8)	202 (40.2)	
Leisure-time physical activity, h/week					
0.0–2.5	161 (32.1)	210 (41.8)	211 (42.0)	238 (47.3)	0.0001
2.6–5.0	160 (31.9)	146 (29.0)	136 (27.1)	139 (27.6)	
> 5.0	181 (36.0)	147 (29.2)	155 (30.9)	126 (25.1)	
Smoking status					
Never	279 (55.6)	276 (54.9)	304 (60.5)	279 (55.5)	0.01
Former	196 (39.0)	172 (34.2)	159 (31.7)	171 (34.0)	
Current	27 (5.4)	55 (10.9)	39 (7.8)	53 (10.5)	
Body mass index, kg/m^2					
Normal, 18.5–24.9	331 (65.9)	311 (61.8)	319 (63.5)	312 (62.0)	0.04
Overweight, 25.0–29.9	131 (26.1)	146 (29.0)	139 (27.7)	122 (24.3)	
Obese, ≥ 30	40 (8.0)	46 (9.2)	44 (8.8)	69 (13.7)	
Diastolic blood pressure, mmHg, mean (SD)	78.3 (9.3)	79.1 (9.5)	80.4 (9.7)	80.3 (9.9)	0.001
Systolic blood pressure, mmHg, mean (SD)	126.7 (15.9)	127.2 (16.4)	129.5 (17.1)	128.7 (16.8)	0.02
Perceived (subjective) hearing loss	219 (43.6)	194 (38.6)	175 (34.9)	182 (36.2)	0.02
Cannot carry a conversation in a noisy setting	164 (32.7)	129 (25.7)	129 (25.7)	120 (23.9)	0.01
Frequently asking for repetition	95 (18.9)	98 (19.5)	80 (15.9)	82 (16.3)	0.34
Turning up volume on television/radio	85 (16.9)	86 (17.1)	68 (13.6)	82 (16.3)	0.38

*The data obtained during the first 2 years of follow-up

Values refer to number (%) except when noted otherwise. *p* values obtained from Chi-squared tests and ANOVA, as appropriate

Dietary Inflammatory Index (DII): higher values reflect increased pro-inflammatory potential of the diet

between diet quality and HL have been reported in the literature [30], further research is nonetheless warranted.

Prior studies have associated increased risk of subjective HL with lower scores on various diet quality indices (AMED, DASH, AHEI-2010, prudent dietary pattern) [6, 31]. It has been argued that dietary patterns high in fruit, vegetables, legumes, whole grains, nuts, fish, and poultry, with moderate alcohol intake and low saturated fat intake may confer protection against vascular compromise and/or cochlear blood flow reduction via reduced inflammation

Table 2 Sociodemographic, lifestyle and health status characteristics of male participants at the time of hearing level assessment, by Dietary Inflammatory Index (DII) quartiles, $N = 1425$

	Dietary Inflammatory Index (DII)				*p*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
n	357	356	356	356	
DII, mean (SD)	− 2.1 (0.8)	− 0.5 (0.3)	0.6 (0.3)	2.4 (0.9)	< 0.0001
Number of 24-h dietary records, mean (SD)*	10.1 (3.2)	10.5 (2.9)	10.6 (2.8)	10.3 (3.1)	0.06
Total energy intake without alcohol, kcal/day, mean (SD)*	2686.8 (574.9)	2414.1 (441.1)	2212.3 (402.0)	1,959.3 (376.6)	< 0.0001
Alcohol intake, g/day, mean (SD)*	30.3 (22.5)	29.8 (21.9)	29.7 (26.4)	27.2 (23.6)	0.31
Active supplementation group (1994–2002)	182 (51.0)	192 (53.9)	187 (52.5)	188 (52.8)	0.89
Age, years, mean (SD)	64.9 (4.9)	64.6 (4.7)	64.1 (4.6)	63.7 (4.2)	0.002
Marital status					
Married/cohabiting	321 (89.9)	314 (88.2)	319 (89.6)	324 (91.0)	0.67
Living alone	36 (10.1)	42 (11.8)	37 (10.4)	32 (9.0)	
Educational level					
Less than high school	95 (26.6)	93 (26.1)	105 (29.5)	118 (33.1)	0.01
High school diploma or equivalent	57 (16.0)	49 (13.8)	70 (19.7)	64 (18.0)	
Associate's degree or equivalent	38 (10.6)	50 (14.0)	47 (13.2)	55 (15.5)	
Undergradute or graduate degree	167 (46.8)	164 (46.1)	134 (37.6)	119 (33.4)	
Occupational category					
Homemaker, disabled, unemployed	9 (2.5)	6 (1.7)	12 (3.4)	13 (3.7)	0.53
Employed, self-employed	63 (17.7)	73 (20.5)	77 (21.6)	71 (19.9)	
Retired	285 (79.8)	277 (77.8)	267 (75.0)	272 (76.4)	
Leisure–time physical activity, h/week					
0.0–2.5	86 (24.1)	94 (26.4)	108 (30.3)	117 (32.9)	0.02
2.6–5.0	92 (25.8)	83 (23.3)	105 (29.5)	83 (23.3)	
> 5.0	179 (50.1)	179 (50.3)	143 (40.2)	156 (43.8)	
Smoking status					
Never	110 (30.8)	130 (36.5)	105 (29.5)	95 (26.7)	0.12
Former	219 (61.4)	197 (55.3)	213 (59.8)	225 (63.2)	
Current	28 (7.8)	29 (8.2)	38 (10.7)	36 (10.1)	
Body mass index, kg/m^2					
Normal, 18.5–24.9	147 (41.2)	143 (40.2)	112 (31.5)	124 (34.9)	0.01
Overweight, 25.0–29.9	161 (45.1)	178 (50.0)	199 (55.9)	171 (48.0)	
Obese, ≥ 30	49 (13.7)	35 (9.8)	45 (12.6)	61 (17.1)	
Diastolic blood pressure, mmHg, mean (SD)	81.8 (8.5)	83.0 (9.1)	83.4 (9.8)	82.9 (10.1)	0.14
Systolic blood pressure, mmHg, mean (SD)	136.7 (15.6)	137.8 (16.5)	137.8 (16.4)	138.0 (17.1)	0.71
Perceived (subjective) hearing loss	184 (51.5)	167 (46.9)	176 (49.4)	189 (53.1)	0.38
Cannot follow a conversation in a noisy setting	126 (35.3)	128 (36.0)	122 (34.3)	138 (38.8)	0.63
Frequently asking for repetition	84 (23.5)	71 (19.9)	82 (23.0)	82 (23.0)	0.65
Turning up volume on television/radio	100 (28.0)	76 (21.3)	85 (23.9)	105 (29.5)	0.05

*Data obtained during the first 2 years of follow-up

Values refer to number (%) except when noted otherwise. *p* values obtained from chi-squared tests and ANOVA, as appropriate

Dietary Inflammatory Index (DII): higher values reflect increased pro-inflammatory potential of the diet

and blood pressure, beneficial blood lipid profiles, and endothelial function support [6]. Indeed, prudent/healthy dietary patterns have been associated with reduced CRP, E-selectin, IL-6, fasting insulin, and glucose concentrations and with increased insulin sensitivity [32, 33].

In this study, the inflammatory potential of the overall diet was estimated by the DII (and the energy–density DII in a sensitivity analysis) which has consistently shown dietary pattern differentiation similar to that obtained with other diet quality indices, such as AHEI, HEI-2010, and DASH

Table 3 Multivariable logistic regression analysis of the sex-specific associations between Dietary Inflammatory Index (DII) and subjective hearing loss

	Cannot carry a conversation in a noisy setting (Cases: 514 M/542 F)		Frequently asking for repetition (Cases: 319 M/355 F)		Turning up volume on television/radio (Cases: 366 M/321 F)		Perceived hearing loss summary score (Cases: 716 M/770 F)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Males								
Model 1	**1.10**	**(1.02, 1.18)**	1.04	(0.95, 1.13)	**1.09**	**(1.01, 1.18)**	1.06	(0.99, 1.14)
Model 2 (Q1 = reference)								
Q2 vs. Q1	1.17	(0.85, 1.60)	0.86	(0.59, 1.24)	0.81	(0.57, 1.16)	0.92	(0.67, 1.24)
Q3 vs. Q1	1.13	(0.80, 1.58)	1.03	(0.70, 1.50)	1.02	(0.70, 1.48)	1.05	(0.76, 1.45)
Q4 vs. Q1	**1.48**	**(1.03, 2.12)**	1.10	(0.73, 1.65)	**1.53**	**(1.03, 2.26)**	1.31	(0.92, 1.85)
Females								
Model 1	**0.92**	**(0.87, 0.98)**	0.96	(0.90, 1.03)	1.03	(0.95, 1.10)	0.95	(0.90, 1.01)
Model 2 (Q1 = reference)								
Q2 vs. Q1	**0.74**	**(0.56, 0.98)**	1.01	(0.74, 1.40)	1.10	(0.79, 1.55)	0.86	(0.66, 1.11)
Q3 vs. Q1	**0.74**	**(0.55, 0.98)**	0.81	(0.58, 1.14)	0.88	(0.61, 1.26)	**0.74**	**(0.57, 0.97)**
Q4 vs. Q1	**0.69**	**(0.50, 0.93)**	0.84	(0.59, 1.21)	1.19	(0.82, 1.73)	0.83	(0.63, 1.10)

CI confidence interval, *F* females, *M* males, *OR* odds ratio, *Q* quartile

Both models adjusted for supplementation group (1994–2002), age, educational level, employment status, body mass index, systolic and diastolic blood pressure, physical activity, number of 24 h dietary records, dietary energy intake (without alcohol), alcohol intake, and smoking status

Model 1: DII modeled on a continuous scale; Model 2: DII modeled as sex-specific quartiles

Table 4 Multivariable logistic regression analysis of the sex-specific associations between the energy–density Dietary Inflammatory Index (DII) and subjective hearing loss: sensitivity analysis

	Cannot carry a conversation in a noisy setting (Cases: 514 M/542 F)		Frequently asking for repetition (Cases: 319 M/355 F)		Turning up volume on television/radio (Cases: 366 M/321 F)		Perceived hearing loss summary score (Cases: 716 M/770 F)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Males								
Fully-adjusted model	**1.08**	**(1.01, 1.17)**	1.04	(0.96, 1.13)	1.08	(0.99, 1.17)	1.06	(0.98, 1.13)
Females								
Fully-adjusted model	**0.93**	**(0.87, 0.98)**	0.97	(0.90, 1.04)	1.03	(0.95, 1.11)	0.96	(0.91, 1.02)

CI confidence interval, *F* females, *M* males, *OR* odds ratio

Models adjusted for supplementation group (1994–2002), age, educational level, employment status, body mass index, systolic and diastolic blood pressure, physical activity, number of 24 h dietary records, dietary energy intake (without alcohol), alcohol intake, and smoking status

[34]. The DII is a validated summary measure of diet-associated inflammation; it has been studied internationally with respect to its association with various physical and mental health outcomes, such as cancer, cardiovascular disease, asthma, cognitive performance, depression, sleep latency, maternal and child health, aging, and mortality [21, 35–38]. This analysis thus extends evidence about the predictive association of DII with age-related hearing impairment.

Mechanistic evidence from animal models has highlighted the tendency of the mammalian inner ear to lose sensory cells with advancing age [39] as a result of chronic inflammation, oxidative stress, altered antioxidant enzyme levels, and the triggering of apoptotic pathways [40]. The mesenchymal region of the cochlea is likely a common site of inflammation [41] and a correlation has been demonstrated between pro-inflammatory cytokine concentrations and hearing thresholds after noise exposure [42]. In humans, a phenomenon termed "inflammaging" and referring to prevalent chronic inflammation in the elderly, has been studied with respect to HL; an age-dependent association has been reported between a higher white blood cell count and worse hearing level [13]. Animal models have also underscored the potential role of the diet in reducing the magnitude of age-related cochlear degeneration [43]. Next, a long-term high cholesterol and/or high-fat diet has been shown to induce HL via oxidative stress, increasing reactive oxygen species, mitochondrial damage, inner ear apoptosis and vascular compromise [44, 45]. Our models were controlled for total energy intake (along with other factors), which supports a potential causal link between long-term dietary pattern exposure and HL.

The main outcome in this study was subjective HL, which has been moderately correlated with objective HL measures [8, 9, 46]. We modeled a subjective HL summary score as well as three individual HL items, some of which could be perceived as more factual (i.e., inability to carry a conversation in a noisy setting) than others (i.e., television/radio volume which might not be perceived as loud even when turned up). Self-perceived hearing handicap has been linked to a reduced quality of life to a greater extent than audiometrically-assessed HL [7]. Prior research has shown, for example, that fewer than a quarter of those with moderate to profound HL ($\geq$41 dB) perceived themselves as being hearing-handicapped [47]. A population-based study with elderly participants revealed that simply being aware of one's hearing disability was longitudinally associated with worsening functional performance and selective attention, global cognitive deterioration, and depressive symptoms [48].

Two limitations of the present prospective study pertain to the absence of hearing level data at baseline and the fact that DII might have changed over time. At inclusion, participants were generally healthy, middle-aged volunteers (mean ages of 51.3 and 46.6 years among males and females, respectively) and we could speculate that the potential prevalence of any hearing-related conditions (and presbycusis in particular) was likely low. Another limitation pertains to the absence of information about the types of presbycusis in the study sample. Next, despite the large number of covariates included in the adjusted analysis, other potential confounders, such as tinnitus, noise exposure and genetic factors, were not included in the models. In turn, similar to other a priori indices, DII might be subject to some limitations, such as arbitrary selection of components and scoring methods [49]. In this study, DII was computed on the basis of 35 dietary parameters (versus anywhere from 27 to 30 in most other studies), yet the original index was based on 45 dietary parameters. It should also be pointed out that the lack of a dose–response relationship might be partly interpreted as possible evidence for a nonlinear association between the inflammatory potential of the diet and subjective hearing loss, to be investigated by future research. A strength of this study was the use of a large sample of middle-aged and older adults recruited from the general population. Yet, the question of external validity remains, given that the participants had engaged in a long-term nutrition-focused research and might therefore not be representative of the general French population.

As society ages, the number of individuals suffering from HL will grow. This tendency is alarming, given evidence of the association of HL with accelerated cognitive decline, poorer physical functioning, increased risk for falls, poor physician–patient communication, and poor adherence to treatment regimens [50]. The findings among males revealed that a pro-inflammatory diet could increase risk of age-related HL, providing support for the long-term preventive potential of a healthy diet. However, the findings among females were unexpected and could not be attributed to sex-specific differences in energy density; thus, they merit further investigation. Likewise, future research could replicate the models using objective HL measures. This study could inform future targeted HL prevention efforts and could serve as impetus for epidemiological research in the context of both sensory disability and aging.

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Author contributions SH, PG and EKG: SU.VI.MAX project conception, development of research plan, study oversight, data collection management; NS, JRH, and MDW: developed the DII®; SP, PG and EKG: developed the hearing data collection protocol and coordinated data collection; CJ, MT, and EKG: coordinated the calculation of DII within the SU.VI.MAX cohort; VAA: conducted research (literature review and statistical analysis) and led the writing; SP, JRH and EKG: provided analytical and theoretical guidance; all authors made major contributions to writing the manuscript, read and approved the final version; VAA: had primary responsibility for final content.

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Data availability Data described in the manuscript will be made available upon request, pending application and approval.

Code availability The SAS programs will be made available upon request, pending application and approval.

Declarations

Conflict of interest The Dietary Inflammatory Index (DII®) is a registered trademark of the University of South Carolina. JR Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the DII from the University of South Carolina in order to develop computer and smartphone applications for patient counseling and dietary intervention in clinical settings. MDW and NS are employees of CHI. These activities have no direct bearing on the use of the DII as a research tool. VAA, SP, CJ, MT, SH, PG, and EKG have no conflicts of interest to report.

Ethics approval All procedures were approved by the Ethics Committee for Studies with Human Participants of Paris-Cochin Hospital (CCPPRB #706 and #2364) and the National Commission on Informatics and Liberty (CNIL #334641 and #907094).

Consent to participate Written informed consent was obtained from each participant prior to enrollment.

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