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Title

Patterns of polyphenol intake and risk of depressive symptomatology in a population-based cohort of older adults.

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Polyphenol intake and depressive symptomatology

List of abbreviations

3C: Three-City, ATC: Anatomical Therapeutic Chemical, BDNF: Brain-Derived Neurotrophic Factor, BMI: Body Mass Index, CES-D: Center for Epidemiologic Studies-Despression, CHU : Centre Hospitalier Universitaire, CI: Confidence Interval, DS: Depressive Symptomatology, HR: Hazard Ratio, MAO: Monoamine Oxidase, MMSE: Mini Mental State Examination, NHS: Nurses Health Study, OR: Odd Ratio, PCA: Principal Component Analysis, PP: Polyphenols, RCT: Randomised Controlled Trials, SD: Standard Deviation, WHO: World Health Organization.

ABSTRACT

Background & Aims: Current evidence suggests that some isolated polyphenols (PP) may exert promising effects for the risk of depression in young adults, however studies among older adults remain limited. The aim of the current study was to examine the prospective association between patterns of PP intake and the risk of depressive symptomatology (DS) in older adults.

Methods: The study sample was based on the Three-City (3C) Bordeaux cohort of adults aged 65 years and over and without DS at the time of recruitment. The intakes of PP, summarised into 21 PP classes, were determined using a 24-hour recall combined with the Phenol-Explorer database. In addition, the patterns of PP intake were identified by a Principal Component Analysis (PCA). DS was evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D) over a period of 15 years with a reassessment every 2-3 years. The incident DS was reported for CES-D score ≥16 and/or the use of antidepressant treatment. The association between the patterns of PP intake at baseline and the risk of DS was computed using multivariate random-effect logistic regression models.

Results: Among the 1,074 participants (mean age 75.7y, SD 4.8y), 423 (39.4%) developed a DS during the follow-up. Distinct patterns of PP intake were identified, explaining up to 50% of the variance. The two first patterns, mainly driven by stilbenes and dihydroflavonols and by hydroxyicnnamic acid and alkylmethoxyphenols respectively, were not associated with the odds of DS. Furthermore, a higher score on the third pattern, mainly driven by monomeric flavanols and theaflavins, was associated with a significant 27% lower risk of DS over time (Odd Ratio=0.73, 95% Confidence Interval [0.55;0.97]).

Conclusion: This prospective study suggested that a pattern high in monomeric flavanols and theaflavins intakes, mainly provided by tea, was associated with a reduced risk of DS in older adults. These results provide promising evidence on combined PP intakes that would require further confirmation in other samples.

Key words: Polyphenol, dietary patterns, depressive symptomatology, older adults, Cohort, Three-City.

INTRODUCTION

According to the World Health Organization (WHO), depression affected 380 million people worldwide in 2019 (1), leading to identify this common disease as the most expensive health condition in 2020 (2). Depression is mainly characterised by a persistent feeling of sadness, a loss of interest and pleasure, and is associated with numerous secondary symptoms (e.g., fatigue, appetite and sleep disturbances, suicidal thoughts). Various degrees of severity results in different definition of the disease (3,4), and pejorative life events, such as widowhood, loss of functional capabilities and social isolation, are increasing the risk for depression particularly in older adults. As a consequence, the prevalence of depression in adults over 50 years old ranges from 6% to nearly 17% compared with less than 5% in the general population (5,6). Available antidepressant treatments exhibit unequal efficacy, one third of adults being unresponsive and even more in older adults, half being resistant to the treatments (7,8). Furthermore, the frequent side effects of the drugs are often exacerbated by the polypharmacy in older adults (9). Therefore, it is crucial to develop relevant preventive approaches to decrease the risk of depressive symptomatology in the older adults. Previous studies in this field have identified several modifiable factors that play a role in the diminution of the risks of depression including physical activity, good social support and a better self-rated health (10), as well as healthy nutritional habits. These healthy habits have their importance over the lifespan and appear equally significant in older adults. For instance, a greater adherence to the Mediterranean diet, a greater consumption of fruits and vegetables and some beverages, such as tea and coffee, have been inversely associated with the risk of depression in several epidemiological studies (11–18). Interestingly, all these food groups are particularly rich in polyphenols (PP), naturally occurring phytochemical compounds exclusively synthesised by plants and exhibiting antioxidant and anti-inflammatory properties (19–21). The large family of

polyphenols (>8000 species) has been divided into two main categories, flavonoids and non-flavonoids, which are further divided into classes with specific molecular structures (19–21). Several recent cross sectional studies have illustrated the benefits of higher consumption of distinct PP on the lower prevalence of depression in heterogeneous populations (22–25). However, to the best of our knowledge, only one prospective observational study has examined the association between PP intakes (limited to flavonoids) and the risk of depression in middle-aged and older women. This study, conducted on the large Nurses Health Study (NHS) and NHS II cohorts, reported that a higher consumption of flavonols, flavones and flavanones was independently and significantly associated with a reduced risk of depression over a 10-year period (26). On the other hand, in older women, higher intake of total flavonoids, polymeric flavonoids and proanthocyanidins was significantly associated with a reduced risk of depression. In addition, some randomised controlled trials (RCT) have observed beneficial effects of specific PP or PP rich-foods on depression, such as isoflavones, monomeric flavanols, proanthocyanidins, resveratrol, curcumin, or chamomile, soy, green tea, nuts, cocoa… (27,28). However, most of these RCTs only evaluated the potential therapeutic properties of PP rather than their preventive effects on depression. Additionally, available observational longitudinal study and clinical trials have been limited by the study of a single PP or PP rich-food, while concomitant exposures to several PP with potential complementary biological properties have not been prospectively explored in relation to depression. Finally, the particular feature of depression, i.e., its potentially transient nature over time, has not yet been taken into account in studies focusing on this topic.

Therefore, the aim of the present study was to examine the prospective association between patterns of PP intake and the risk of depressive symptomatology (DS) in older adults enrolled in the Three-City (3C) cohort.

METHODS

Population

The 3C cohort is a population-based cohort on 9,294 non-institutionalised people aged 65 and over, recruited in 1999 from electoral rolls of three French cities: Bordeaux (n=2,104), Dijon (n=4,931) and Montpellier (n=2,259). Eight follow-up visits, consisting of face-to-face interviews at home for each participant, were performed every 2-3 years until 2018. The study protocol was approved by the Committee for the Protection of Persons Participating in Biomedical Research of the Centre Hospitalier Universitaire (CHU) of Kremlin-Bicêtre and a free and informed consent was signed by each participant. The entire protocol and methodology of the 3C cohort have been previously detailed elsewhere (29).

Study sample

Participants from the Bordeaux 3C cohort completed a full dietary survey in addition to general questionnaires. Additional inclusion criteria were applied to reach the final study sample: at inclusion for the present study, participants had to have information on PP intake and DS, without presenting DS at entry and 2 years earlier (at 3C recruitment), as verified by the Center for Epidemiologic Studies-Depression (CES-D) scale (CES-D score≥16, detailed later) and by their use of antidepressants; they had to be reviewed at least once with a DS assessment during follow-up and in addition, they had to be free from dementia at baseline.

Polyphenol intake

At the Bordeaux center, a 24-hour dietary recall was administered by face-to-face interviews performed by dieticians in the participants' home in 2001-2002, considered as the baseline for the present study. Participants were asked to report all meals and drinks consumed the day before the

interview (excluding weekend meals), as well as the quantities eaten, using a portion photograph manual. As previously done (30), daily PP intake was assessed by matching food and beverages intakes with the Phenol-Explorer composition database (version 3.6). Based on more than 1,300 scientific publications, Phenol-Explorer is the first comprehensive database on PP content of foods and contains information on more than 500 different PP in over 400 foods (31). In the current study, 396 different PP compounds were consumed and grouped into 21 main classes: proanthocyanidins, monomeric flavanols, theaflavins, flavanones, flavonols, anthocyanins, flavones, chalcons, isoflavones, dihydrochalcons, dihydroflavonols from flavonoids category, and hydroxybenzoic acid, hydroxycinamic acid, hydroxyphenylacetic/phenylpropanoic acid, stilbenes, lignans, tyrosols, alkylmethoxyphenols, alkylphenols, hydroxybenzaldehydes and other PP of the non-flavonoid class.

Depressive Symptomatology

DS was assessed using the CES-D scale in a face-to-face interview conducted by a neuropsychologist at each follow-up visit. This 20-items scale assessed the frequency of depressive symptoms during the previous week (from « never » to « always », rated from 0 to 3), leading to a total score ranging from 0 to 60. A validated, widely used international cut-off of 16 or over confirmed a DS (32). The use of antidepressant treatment corresponding to the WHO Anatomical Therapeutic Chemical (ATC) classification “N06A” was recorded from the inventory of all drugs consumed at each follow-up visit (33). The CES-D cut-off score and the use of antidepressant treatment were combined to estimate the occurrence of DS (the primary endpoint of the present study) at each follow-up visit.

Other variables

Socio-demographic and lifestyle information collected at baseline included: sex, age, living conditions (living alone, in couple and cohabitation), educational level (no study or elementary, secondary, high school and university), monthly income (<1,500€, 1,500-2,250€, ≥2,250€ and refused to answer), tobacco consumption (number of pack-years), body mass index (BMI) (<25, 25-30 and ≥30 kg/m²), regular physical activity (yes or no, considered through a sport or daily leisure activities as for example walking, gardening or fishing) and total energy intake (in kcal/day). Among health characteristics, the Mini Mental State Examination (MMSE) score was used to assess overall cognitive performances and multimorbidity was considered when participants exhibited two or more of the following: hypertension, diabetes, hypercholesterolemia, angina, cardiac rhythm disorders, arteritis, cardiac failure, myocardial infarction, hospitalization for stroke, asthma, Parkinson's disease, dyspnea, osteoporosis, cancer and dementia. These disorders were self-reported, apart from dementia, which was diagnosed clinically by a neuropsychologist.

Statistical Analysis

All statistical analyses were performed with R Software (R version 4.1.1, RStudio environment) and statistical significance was set at $p<0.05$. The socio-demographic characteristics of the study sample were described according to the quartiles of total daily PP intake. Chi-square tests for qualitative variables and Analysis of Variance for quantitative variables (non-parametric ones for those with asymmetric distribution) were used. Aggregate PP consumption in 21 classes was also described by sex using Student's t-test (or Welch's test in the case of unequal variances).

Patterns of dietary polyphenol intake

Principal Component Analysis (PCA) was used to extract dietary PP patterns derived from the 21 PP classes. PCA method is widely used in multidimensional nutritional data to identify dietary

patterns (34). This data-driven technique reduces the dimensionality of the dataset and aggregates correlated variables to derive common components, in this case, dietary PP intakes, by maximising the variability of the study sample. This still results in a loss of information, while approaching the real-life practices of combined consumptions of isolated PP. Both the retention criteria of eigenvalues greater than 1 and the Cattell criteria were used to select the number of principal components (i.e. patterns) (35). For each selected pattern, the main classes of PP were highlighted for absolute loadings greater than or equal to 50 %. A correlation between PP intake from identified principal components and food intakes was performed to determine the main food sources of PP intake patterns in the present study.

Association between patterns of polyphenol intake and risk of DS

A multivariate random-effect logistic regression model was used to explore the relationships between the patterns of PP intake at baseline and the risk of DS over time. The model was adjusted for the relevant potential confounders selected from the scientific literature using a directed acyclic graph: age, sex, living conditions, tobacco consumption, educational level, regular physical activity, daily energy intake, BMI and multimorbidity were included. The random-effect logistic regression model is appropriate for assessing the risk of DS as a binary outcome and for modelling repeated assessments (and possible reversibility) during the follow-up (36). Time was introduced as a simple effect and two random effects were included: a random intercept, accounting for the heterogeneity between individuals at baseline, and a random slope, accounting for the inter-individual variability over time (detailed in **Supporting Information Method S1**). The model assumptions were tested and statistical significance was set at $p<0.05$.

Additional analyses

Firstly, DS was defined by the use of antidepressant treatments and/or alternative CES-D thresholds, i.e. validated sex-specific French cut-offs of the CES-D: score ≥17 for men and ≥23 for women (37). Secondly, as the PP intake is assumed to differ between men and women, we also extracted dietary PP patterns separately for each sex and performed main analyses stratified on sex.

Missing data

To limit exclusions due to missing values, a multiple imputation was performed on the retained confounders with missing data, i.e. tobacco consumption (1.5% of missing data), regular physical activity (15.5%) and BMI (0.9%) using the R package MICE (Multivariate Imputation via Chained Equations) (38). This method assumes that data are randomly missing and that each variable is associated with an imputation model conditionally to the other variables in the dataset.

RESULTS

Sample selection

Among the 2,104 participants from the 3C Bordeaux sub-cohort, 1,755 participated in the dietary survey at baseline and were eligible for the present study. From 1,755 participants included at baseline, we excluded participants with DS identified at baseline (n=153), or 2 years earlier (based on CES-D score≥16 and/or antidepressant treatment) (n=358), missing data on DS at baseline (n=30) or no DS assessment during the follow-up (n=104), missing data on PP intake (n=30) and history of dementia at baseline (n=6), leading to a study sample of 1,074 individuals (**Figure 1**). The median of follow-up time was 11.5 years (minimum 1.0 year and maximum 16.4 years), during which 551 participants died and 130 dropped-out, resulting in 393 individuals seen at the 15-y wave (36.6% of the participants included at baseline).

Descriptive characteristics

The study sample included 56.8% of women and was 75.7 years old (standard deviation (SD): 4.8) on average. More than half of the sample (58.6%) were living with a partner, 48.5% had attained primary or secondary school education and 37.2% reported a monthly income of less than 1,500€ (**Table 1**). The participants smoked an average of 9.4 pack-years and consumed 9.8 glasses of alcohol per week. In addition, more than a third of the study sample (38.0%) regularly practiced a physical activity, 16.2% of the sample had a BMI higher than 30 kg/m² and consumed 1,746 kcal/day on average. Regarding health characteristics, the MMSE score was 27.8 on average and 53.8% of participants were affected by multimorbidity. Finally, the CES-D score at baseline was 4.9 on average (Table 1).

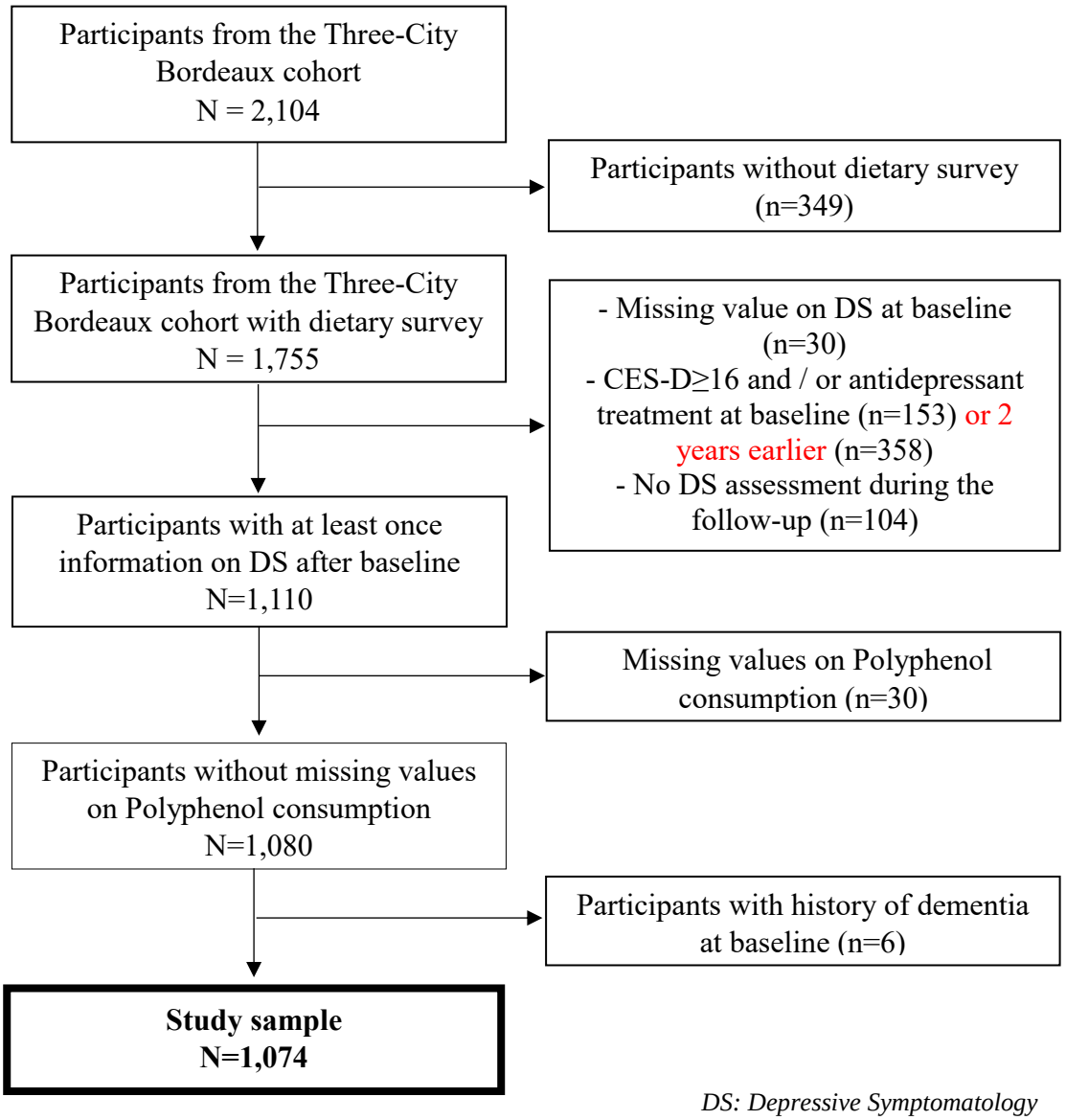

Figure 1: Flow chart for the study of the association between patterns of polyphenol intake and the risk of depressive symptomatology, Three-City Bordeaux cohort, 2001-2017

Participants consumed about 1,092 mg (SD: 560 mg) of total PP per day on average. Considered as quartiles, the daily intake of low PP consumers (first quartile (Q1)) was 483 mg (SD: 157 mg) on average, that of low to moderate PP consumers (second quartile (Q2)) was 856 mg (SD: 102 mg) on average, that of moderate PP consumers (third quartile (Q3)) was 1,179 mg (SD: 98.4 mg) on average and that of high PP consumers (forth quartile (Q4)) was 1,850 mg (SD: 446 mg) on average. (Table 1). We observed that the highest total PP consumers (Q4) were mainly men, more often lived in couples, had higher level of education, consumed more often tobacco and alcohol, and had higher daily energy intake and higher MMSE scores on average than the lowest PP consumers (Q1). They also had lower CES-D score on average than the lowest consumers (4.3 *vs* 5.1 respectively). Mean age, monthly incomes, BMI, prevalence of regular physical activity and multimorbidity were similar across quartiles of total PP intakes.

Table 2 described the 21 main classes of dietary PP consumed at baseline by sex. Men had higher consumption of total PP than women (1,234 mg SD: 574 mg *vs* 984 mg SD: 524 mg, respectively). Regardless of sex, the main classes of PP consumed were hydroxicinnamic acid (515 mg/day), followed by proanthocyanidins (288 mg/day) and monomeric flavanols (84 mg/day). The mean daily intake of flavanones, flavones, isoflavones, hydroxybenzoic acid, alkylmethoxyphenols and other PP were not significantly different between men and women. However, men had higher daily intakes of all other classes of PP, except for theaflavins whose intakes were greater for women (5.4 mg (SD: 9.6 mg) *vs* 2.4 mg (SD: 5.8 mg) in men).

Patterns of dietary polyphenol intake

In the overall study sample, we selected 3 distinct dietary PP patterns identified by the PCA method (**Table 3**), explaining 45.3% of the variability of the 21 PP classes consumed. The 3 components (i.e., patterns) were scores ranging from 0 to 8, and a higher score indicating greater adherence to

the PP pattern (i.e. a higher intake of the main PP classes for each pattern). The first principal component (explaining 23.7% of the variability) was a pattern characterized by high intakes of stilbenes, dihydroflavonols, hydroxybenzaldehydes, lignans, tyrosols, hydroxyphenylacetic and hydroxyphenylpropanoic acid, proanthocyanidins and anthocyanins, of which main food source was red wine. The second principal component (explaining 13.1% of the variability) was a pattern defined by high intakes of hydroxycinnamic acid, alkylmethoxyphenols and other PP and by a lower intake of theaflavins and monomeric flavanols. The three main PP classes highly consumed in this pattern were derived from high consumptions of coffee whereas the two main PP classes lower consumed in this pattern derived mainly from tea consumption. Then, the third principal component (explaining 8.5% of the variability) was a pattern defined by high intakes of monomeric flavanols and theaflavins, mainly derived from tea consumption.

Depressive Symptomatology

DS was identified for 423 participants (39.4 %) during the follow-up. Of whom, 230 (21.4%) participants had a CES-D score ≥16 at least once during follow-up, 110 (10.3%) used antidepressant treatment at least once during follow-up and 83 (7.7%) had both CES-D score ≥16 and antidepressant treatment use during follow-up.

Pattern of dietary polyphenol intake associated with risk of DS

The association between the three principal components derived from PP intake and the risk of DS was assessed separately and controlled for sex, living conditions, educational level, tobacco consumption, daily energy consumption, regular physical activity, BMI and multimorbidity. There was no association between higher scores on the principal components 1 or 2 and the risk of DS over time (Odd Ratio (OR)=1.00, 95% Confidence Interval (CI) [0.82;1.22], p=0,990 and

OR=0.98, 95% CI [0.79;1.21], p=0.838 for each additional point of the 1st and 2nd components respectively) (**Table 4**). However, higher scores on the 3rd component (i.e., mainly higher monomeric flavanols and theaflavins intakes) were significantly associated with a lower risk of DS over time. Indeed, for a one point increase in the pattern score, a 27% lower risk of DS was observed (OR=0.73, 95% CI [0.55;0.97], p=0.027) (Table 4).

Additional analyses

Using an alternative definition of DS, based on the gender-specific CES-D cut-offs (i.e., CES-D score ≥17 for men and a CES-D score ≥23 for women) and / or use of antidepressant treatments, 338 (31.5%) participants were identified as having DS over time. As in the main analysis, higher scores on principal components 1 or 2 were not significantly associated with the reduced risk of DS (**Table 5**). However, for each additional point of the 3rd pattern score, the risk of DS was significantly lower by 41% over time, after adjustment on all potential confounders (OR=0.59, 95% CI [0.39;0.88], p=0.010) (Table 5).

When PCAs were conducted separately for men and women, the principal components 1 and 2 were similar to those observed in the whole study sample, whereas the 3rd principal component was different than that derived from the entire study sample. For men, the 3rd principal component was a pattern characterized by low intakes of hydroxyphenylcetic and hydroxyphenylpropanoic acid and tyrosols, i.e., PP classes mainly derived from red wine whereas for women, the 3rd pattern was characterised by high intakes of monomeric flavanols, theaflavins and flavonols, mainly derived from tea and red wine consumptions (**Supporting Information Table S1 & Table S2**). As in the main analysis of the entire study sample, higher scores on principal components 1 or 2 were not significantly associated with a reduced risk of DS for either sex. Additionally, higher scores on principal component 3 were not associated with the risk of DS in men. However, in women, higher

scores on the 3rd component were significantly associated with lower risk of DS over time (**Supporting Information Table S3**).

DISCUSSION

In the present study, we identified three patterns of PP intake at baseline in older adults, one of which, mainly characterised by high intake of monomeric flavanols and theaflavins, provided mainly by tea, was associated with a significant reduced risk of DS over 15-years of follow-up. Each additional point on this pattern score was significantly associated with a 27% reduction in the risk of DS, independent of the main confounding factors including sex, BMI, regular physical activity and multimorbidity. Using an alternative definition of DS based on the sex-specific CES-D threshold and/or the use of antidepressant treatment, we observed an even lower risk of DS, up to 41%. To our knowledge, this is the first prospective study reporting an inverse association between a data-driven pattern of PP intake and the risk of DS in older adults, considering repeated assessment of DS over time.

Comparison to the literature

The relationship between PP intake and DS in older adults had already been explored in several studies, although mainly cross sectional. Of these, 6 out of 20 cross-sectional studies reported an inverse association between tea consumption, or monomeric flavanols and theaflavins compounds and depression (25,27). It should be noted that only one prospective study in the NHS cohort had explored the association between individual PP intake at baseline, and the risk of DS in older adults. This cohort included about 45,000 US women aged ≥65 years followed for 10 years and reported that higher consumption of total flavonoids, polymeric flavonoids or proanthocyanidins was separately associated with a significant decreased risk of DS (quintile 5 *vs* quintile 1: Hazard Ratio (HR)=0.89, 95% CI [0.82;0.96], p-trend=0.003 ; HR=0.88, 95% CI [0.82;0.96], p-trend<0.001 and HR=0.83, 95% CI[0.77;0.90], p-trend<0.001 respectively) (26). Using a semi-quantitative food frequency questionnaire matched to the United States Department of Agriculture (USDA) database,

flavonoid intake and PP class intakes were assessed individually in the NHS cohort, in contrast to the present study in which we examined several PP classes, consumed concomitantly in the diet. Moreover, in the NHS cohort, the risk of DS was defined as the first occurrence of self-reported clinical depression (i.e., clinical diagnostic and/or regular use of antidepressants) over time, using a statistical approach that did not account for the potential change of depression over time available with repeated measures. Notably, no association was found among middle-aged women in the NHS II cohort, as in the combined NHS and NHS II cohorts.

Despite the paucity of epidemiological studies, two RCTs have already examined the effects of increased flavanol intake on depression (39,40). Patients with depressive symptoms were supplemented with flavanols-rich foods, including monomeric flavanols, theaflavins and proanthocyanidins: a grape seed extract in postmenopausal women (n=91) in an 8-week trial and a cocoa extract in obese adults (n=45) in a 4-week trial. No significant effect on existing depression was demonstrated in these two RCTs which could be partly explained by the small sample sizes and short duration of supplementation. In addition, these RCTs focused on the therapeutic effect of certain PP on depressive symptoms in patients suffering from postmenopausal symptoms or obesity. A single RCT explored the preventive effect of green tea on depression in 46 healthy adults (mean age: 25.7+/- 4.7 years) (41). Depressive symptoms were assessed using two different scales at baseline and at the end of the study, and the treatment groups were comparable in terms of sex, age, education and depressive symptom scores at baseline. The results revealed that supplementation with green tea composed from approximately 80% of monomeric flavanols (estimated by High Performance Liquid Chromatography) over a period of 5 weeks, significantly decreased depressive symptom scores, whereas no difference was observed in the control group. Thus, the results of this trial conducted in healthy adults are consistent with the present findings.

Considerations

In the additional sex-stratified analysis, we observed a significant association between the third pattern of PP intake and the risk of DS only in women. This pattern was characterized by high intakes of monomeric flavanols, theaflavins and flavonols, mainly from tea and red wines consumption. Overall, the results of the present analysis support the potential benefits of monomeric flavanols and theaflavins on the risk of depression, and may explain observed differences between men and women both in their dietary behaviours, i.e., tea intake, and in the expression of depressive symptoms, i.e., the threshold of the CES-D score in relation to sex.

The mechanistic data also support the role of the PP pattern as a possible protector in DS processes. Firstly, monomeric flavanols and theaflavins have been associated with a reduced risk of depressive behaviour in animal models (42–44). Secondly, several studies have suggested a beneficial role of flavanols in two processes targeted by antidepressant treatments, namely monoamine oxidase (MAO) inhibition and the induction of brain-derived neurotrophic factor (BDNF) (4,45–49). Moreover, monomeric flavanols and theaflavins have strong antioxidant and anti-inflammatory properties, whereas oxidative stress and inflammatory processes are known to be biological mechanisms involved in depression (20). Furthermore, some monomeric flavanols have been detected in the brains of mice after a period of supplementation in flavanols rich-food extract (grape and blueberry) (50): a potential neuroprotective effect could also be considered through a decrease of neuroinflammatory processes. In addition, the activities of dietary PP on mood are highly dependent of their bioavailability and absorption, which are themselves affected by the gut microbiota via the gut-brain axis (51,52). However, further investigations are needed to better understand this potential interaction. Finally, another possible interpretation is that the high intake of PP characterizing the 3rd pattern in the present study sample might reflect a pattern of healthier

behaviors and thus represents an indicator of other protective lifestyle factors (e.g., healthier eating habits, appropriate physical activity) that reduces the risk of developing DS in old age.

Limitations and strengths

The present study has some limitations to highlight. Only one 24-hour recall was performed at baseline, leading to a less accurate estimate of PP intakes for a specific individual, whereas this estimate could be considered relevant for the whole group of participants (53). Moreover, PP intakes were assessed only once, and the present results assume that dietary intakes did not change during the follow-up. It has already been reported that dietary intakes of the participants in the 3C Bordeaux study were mostly constant over time (54). In addition, depression was not diagnosed clinically but depressive symptoms were assessed by neuropsychologists using the CES-D scale, a validated scale widely used in epidemiological studies (32). Moreover, we also used antidepressant treatment to define DS, thus limiting misclassification bias, and an alternative threshold of CES-D score was considered in further analyses. However, these treatments may also be prescribed in other clinical conditions than depression, which could have led to an overestimation of the proportion of participants with DS in the present study (55). Secondly, the potential selected confounders were not updated during the follow-up while many changes can have a significant impact on all aspects of daily life, especially in older adults (i.e., widowhood and chronic diseases). Finally, the 3rd pattern of PP identified could reflect a general healthy behavior. As suggested by the description of the study sample, the highest consumers of total PP intake have on average better brain health and higher education, which may induce a potential reverse causality bias. However, we were able to reduce it by excluding DS cases at baseline and 2 years earlier. The strengths of our study are the large sample size, the long follow-up time and the control of major confounders, although residual bias may remain in this observational study. PP intake was estimated using the

Phenol-Explorer database, the most recent comprehensive database which includes a large number of PP and their main food sources (although not all foods are included in the database). We also implemented a PCA that allowed us to assess the combination of PP intakes through patterns. Finally, the random effect logistic regression method allowed us to consider the potential change of DS over time, especially in a repeated measures cohort.

CONCLUSION

In this large prospective cohort of older adults, we observed that a pattern of PP intake characterised by higher intake of monomeric flavanols and theaflavins, mainly provided by tea, was associated with a 27% reduced risk of DS over a 15-year of follow-up period. These results call for further observational studies on this relationship in older adults and using a dietary pattern approach to confirm such association. Further explorations are also needed to better understand the biological mechanisms between the currently identified PP and the physiopathological process of depression.

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Conflict of interest

The authors declare no conflict of interest. Activ’Inside 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.

Author contributions

JB, CP and CF designed research; JB, HP and SL conducted research; CH, CS and CD provided essential materials; JB analyzed data or performed statistical analysis; JB, CP and CF wrote paper; JB had primary responsibility for final content; and all authors have read and approved the final manuscript.

Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request: http://www.three-city-study.com/ancillary-studies.php

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Table 1: *Description of sociodemographic, lifestyle and health characteristics of the study sample at baseline according to the total daily polyphenol intake (in quartiles), from the 3C Bordeaux cohort, 2001 (N=1,074).*

	Overall (n=1,074)	Low consumers (n=269) *≤688 mg/day*	Low to moderate consumers (n=268) *]688mg ; 1,020mg]*	Moderate consumers (n=268) *]1,021mg ; 1,373mg]*	High consumers (n=269) *>1,373mg/day*	*p-value*[1]
	N (%) / Mean +/- SD	N (%) / Mean +/- SD	N (%) / Mean +/- SD	N (%) / Mean +/- SD	N (%) / Mean +/- SD	
Women	610 (56.8)	195 (72.5)	163 (60.8)	136 (50.7)	116 (43.1)	*<0.001*
Age (years)	75.7 +/- 4.8	75.8 +/- 4.8	76.0 +/- 4.9	75.5 +/- 4.9	75.4 +/- 4.6	*0.436*
Living conditions						*0.015*
- Alone	381 (35.5)	109 (40.5)	101 (37.7)	85 (31.7)	86 (32.0)	
- In couple	629 (58.6)	147 (54.6)	142 (53.0)	172 (64.2)	168 (62.5)	
- Cohabitation (family or not)	64 (6.0)	13 (4.8)	25 (9.3)	11 (4.1)	15 (5.6)	
Educational level						*0.013*
- No study or elementary without degree	89 (8.3)	36 (13.4)	25 (9.3)	17 (6.3)	11 (4.1)	
- Elementary with degree or secondary	521 (48.5)	122 (45.4)	130 (48.5)	133 (49.6)	136 (50.6)	
- High school	246 (22.9)	64 (23.8)	63 (23.5)	54 (20.1)	65 (24.2)	
- University	218 (20.3)	47 (17.5)	50 (18.7)	64 (23.9)	57 (21.2)	
Monthly income						*0.065*
- < 1,500 €	399 (37.2)	120 (44.6)	107 (39.9)	83 (31.0)	89 (33.1)	
- 1,500 – 2,250 €	273 (25.4)	62 (23.0)	67 (25.0)	78 (29.1)	66 (24.5)	
- ≥2,250 €	332 (30.9)	70 (26.0)	76 (28.4)	91 (34.0)	95 (35.3)	
- No answer	70 (6.5)	17 (6.3)	18 (6.7)	16 (6.0)	19 (7.1)	
Tobacco consumption (number of packs-year) [a]	9.4 +/-17.9	5.3 +/- 13.3	8.2 +/- 17.7	9.7 +/- 17.7	14.4 +/- 21.3	*<0.001*

	Overall (n=1,074)	Low consumers (n=269) *≤688 mg/day*	Low to moderate consumers (n=268) *]688mg ; 1,020mg]*	Moderate consumers (n=268) *]1,021mg ; 1,373mg]*	High consumers (n=269) *>1,373mg/day*	*p-value*[1]
	N (%) / Mean +/- SD	N (%) / Mean +/- SD	N (%) / Mean +/- SD	N (%) / Mean +/- SD	N (%) / Mean +/- SD	
Weekly alcool consumption (number of glasses)	9.8 +/- 12.1	4.1 +/- 6.6	6.7 +/- 8.5	11.0 +/- 10.8	17.5 +/- 16.1	*<0.001*
Regular physical activity [b]	345 (38.0)	86 (37.7)	78 (36.3)	89 (39.0)	92 (38.8)	*0.930*
- No	563 (52.4)	142 (52.8)	137 (51.1)	139 (51.9)	145 (53.9)	
- Yes	345 (32.1)	86 (32.0)	78 (29.1)	89 (33.2)	92 (34.2)	
- Missing data	166 (15.5)	41 (15.2)	53 (19.8)	40 (14.9)	32 (11.9)	
Daily energy intake (kcal/day)	1,746 +/-543	1,531 +/- 503	1,652 +/- 474	1,811 +/- 519	1,992 +/- 561	*<0.001*
BMI (kg/m²) [c]						*0.233*
- <25	400 (37.6)	96 (36.6)	103 (38.7)	103 (38.6)	98 (36.4)	
- [25 ; 30 [	492 (46.2)	112 (42.7)	119 (44.7)	132 (49.4)	129 (48.0)	
- ≥30	172 (16.2)	54 (20.6)	44 (16.5)	32 (12.0)	42 (15.6)	
MMSE score [d]	27.8 +/- 1.9	27.5 +/- 2.1	27.6 +/- 1.9	27.8 +/- 1.8	28.1 +/- 1.6	*0.004*
Multimorbidity[2]	578 (53.8)	147 (54.6)	159 (59.3)	135 (50.4)	137 (50.9)	*0.137*
CES-D score	4.9 +/- 4.0	5.1 +/- 4.0	5.2 +/- 3.9	5.0 +/- 4.1	4.3 +/- 3.7	*0.035*
Daily polyphenol consumption (mg/day)	1,092 +/- 560	483 +/- 157	856 +/- 102	1,179 +/- 98	1,850 +/- 446	*<0.001*

BMI=Body Mass Index; MMSE=Mini Mental State Examination; CES-D=Center for Epidemiologic Studies-Depression

Missing data for: [a] n=16, [b] n=166, [c] n=10, [d] n=2

[1]p-value from Chi-square tests for qualitative variables and from Analysis of Variance for quantitative variables

[2]2 out of the 15 self-reported disorders among: hypertension, diabetes, hypercholesterolemia, angina, cardiac rhythm disorders, arteritis, cardiac failure, myocardial infarction, hospitalization for stroke, asthma, Parkinson's disease, dyspnea, osteoporosis, dementia and cancer

***Table 2**: Description of daily consumption of polyphenol classes (mg/day) at baseline on the whole study sample and according to the sex, from the 3C Bordeaux cohort, 2001 (N=1,074).*

Polyphenol classes	Overall (1,074)	Men (n=464)	Women (n=610)	*p-value*[1]
	Mean +/- SD	Mean +/- SD	Mean +/- SD	
Flavonoids				
- **Proanthocyanindins**	287.9 +/- 241.6	360.6 +/- 249.2	232.6 +/- 220.2	*<0.001**
- **Monomeric Flavanols**	83.7 +/- 102.7	74.6 +/- 75.5	90.7 +/- 118.9	*0.007**
- **Theaflavins**	4.1 +/- 8.3	2.4 +/- 5.8	5.4 +/- 9.6	*<0.001**
- **Flavanones**	22.6 +/- 39.6	23.9 +/- 41.1	21.5 +/- 38.4	*0.335*
- **Flavonols**	36.2 +/- 45.9	41.4 +/- 47.8	32.2 +/- 44.1	*0.001*
- **Anthocyanins**	57.2 +/- 88.9	77.5 +/- 101.6	41.7 +/- 74.3	*<0.001**
- **Flavones**	11.5 +/- 32.6	13.0 +/- 39.7	10.4 +/- 26.0	*0.218**
- **Chalcons**	0.0 +/- 0.0	0.0 +/- 0.0	0.0 +/- 0.0	*0.001**
- **Isoflavones**	0.9 +/- 10.2	0.4 +/- 5.5	1.3 +/- 12.6	*0.085**
- **Dihydrochalcons**	2.7 +/- 4.4	3.1 +/- 4.7	2.4 +/- 4.1	*0.011**
- **Dihydroflavonols**	7.5 +/- 9.1	12.2 +/- 10.9	3.9 +/- 5.1	*<0.001**
Phenolic Acid				
- **Hydroxybenzoic Acid**	36.9 +/- 120.7	36.9 +/- 98.5	36.8 +/- 135.3	*0.990**
- **Hydroxycinnamic Acid**	514.8 +/- 381.8	553.0 +/- 369.6	485.7 +/- 388.6	*0.004*
- **Hydroxyphenylacetic /phenylpropanoic Acid**	0.3 +/- 0.7	0.5 +/- 1.0	0.2 +/- 0.4	*<0.001**
Stilbenes	4.8 +/- 5.8	7.8 +/- 6.9	2.5 +/- 3.3	*<0.001**
Lignans	0.4 +/- 0.3	0.5 +/- 0.3	0.3 +/- 0.2	*<0.001**
Tyrosols	7.4 +/- 11.3	11.2 +/- 14.1	4.5 +/- 7.3	*<0.001**
Alkylmethoxyphenols	2.5 +/- 2.4	2.7 +/- 2.3	2.4 +/- 2.6	*0.079**
Alkylphenols	6.3 +/- 12.1	7.4 +/- 14.5	5.4 +/- 9.8	*0.010**
Hydroxy Benzaldehydes	1.0 +/- 1.2	1.7 +/- 1.4	0.6 +/- 0.7	*<0.001*
Other polyphenols	3.5 +/- 3.0	3.6 +/- 3.0	3.4 +/- 3.0	*0.169**

Polyphenol classes	Overall (1,074)	Men (n=464)	Women (n=610)	*p-value*[1]
	Mean +/- SD	Mean +/- SD	Mean +/- SD	
Total Polyphenols	1092.2 +/- 560.1	1234.5 +/- 574.0	983.9 +/- 524.4	*<0.001**

*[1]p-value from Student t-test for equal variances and *Welch test for unequal variances*

Table 3: *Three main patterns with loadings derived from Principal Component Analysis, from the 3C Bordeaux Cohort, 2001 (N=1,074).*

Polyphenol pattern 1 **Total Variance: 23.72 %**		**Polyphenol pattern 2** **Total Variance: 13.09 %**		**Polyphenol pattern 3** **Total Variance: 8.48 %**	
Polyphenol class	**Loading (%)**	**Polyphenol class**	**Loading (%)**	**Polyphenol class**	**Loading (%)**
Stilbenes	**0.94**	**Hydroxycinnamic Acid**	**0.77**	**Monomeric Flavanols**	**0.60**
Hydroxy-benzaldehydes	**0.94**	**Alkylmethoxy-phenols**	**0.68**	**Theaflavins**	**0.59**
Dihydroflavonols	**0.94**	**Other polyphenols**	**0.66**	Other polyphenols	0.45
Lignans	**0.76**	Flavanones	0.21	Alkylmethoxy-phenols	0.45
Tyrosols	**0.75**	Flavones	0.15	Hydroxycinnamic Acid	0.43
Hydroxy-phenylacetic/ phenylpropanoic Acid	**0.59**	*Proanthocyanidins*	*-0.06*	Flavonols	0.33
Proanthocyanidins	**0.58**	*Anthocyanins*	*-0.07*	Dihydrochalcons	0.27
Anthocyanins	**0.51**	*Isoflavones*	*-0.11*	Flavones	0.19
Flavonols	0.31	*Flavonols*	*-0.16*	Hydroxybenzoic Acid	0.17
Hydroxycinnamic Acid	0.20	*Lignans*	*-0.19*	Proanthocyanidins	0.16
Monomeric Flavanols	0.17	*Hydroxybenzoic Acid*	*-0.23*	Flavanones	0.15
Other Polyphenols	0.16	***Theaflavins***	***-0.73***	Lignans	0.11
Hydroxybenzoic Acid	0.15	***Monomeric Flavanols***	***-0.73***	*Hydroxy-benzaldehydes*	*-0.08*
Chalcons	0.12			*Dihydroflavonols*	*-0.11*

Polyphenol pattern 1 **Total Variance: 23.72 %**		**Polyphenol pattern 2** **Total Variance: 13.09 %**		**Polyphenol pattern 3** **Total Variance: 8.48 %**	
Polyphenol class	**Loading (%)**	**Polyphenol class**	**Loading (%)**	**Polyphenol class**	**Loading (%)**
Alkylmethoxy-phenols	0.12			*Stilbenes*	*-0.11*
Dihydrochalcons	0.10			*Tyrosol*	*-0.25*
Isoflavones	*-0.07*			*Hydroxy-phenylacetic/ phenylpropanoic Acid*	*-0.26*

Table 4: *Association between the three patterns of polyphenol intake at baseline and the risk of depressive symptomatology over time (i.e. CES-D score ≥ 16 and/or antidepressant treatment), from the 3C Bordeaux cohort, 2001-2017 (N=1,074)*

	OR [95% CI]*	***p-value****
Pattern 1 score (for 1 point rise)***	1.00 [0.82;1.22]	*0.990*
Pattern 2 score (for 1 point rise)***	0.98 [0.79;1.21]	*0.838*
Pattern 3 score (for 1 point rise)***	**0.73 [0.55;0.97]**	***0.027***

** Random-effect logistic regression model with a random intercept and a random slope adjusted for age (included in the model time), sex, living condition, educational level, tobacco consumption, daily energy intake, regular physical activity, BMI and multimorbidity*
*** P-value of the log-likelihood ratio test*
**** Principal components from PCA on 21 polyphenols classes*

Table 5: *Association between the three patterns of polyphenol intake at baseline and the risk of depressive symptomatology over time defined as CES-D≥17 for men and ≥23 for women and/or antidepressant treatment, from the 3C Bordeaux cohort, 2001-2017 (N=1,074)*

	OR [95% CI]*	***p-value****
Pattern 1 score (for 1 point rise)***	0.97 [0.74;1.27]	*0.841*
Pattern 2 score (for 1 point rise)***	0.94 [0.69;1.28]	*0.701*
Pattern 3 score (for 1 point rise)***	**0.59 [0.39;0.88]**	***0.010***

** Random-effect logistic regression model with a random intercept and a random slope adjusted for age (included in the model time), sex, living condition, educational level, tobacco consumption, daily energy intake, regular physical activity, BMI and multimorbidity*
*** P-value of the log-likelihood ratio test*
**** Principal components from PCA on 21 polyphenols classes*

SUPPORTING INFORMATION

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TITLE PAGE

Title

Patterns of polyphenol intake and risk of depressive symptomatology in a population-based cohort of older adults.

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Running head

Polyphenol intake and depressive symptomatology

List of abbreviations

3C: Three-City, CES-D: Center for Epidemiological Studies Depression, CI: Confidence Interval, DS: Depressive Symptomatology, OR: Odd Ratio, PCA: Principal Component Analysis, PP: Polyphenols.

SUPPORTING INFORMATION

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Table S2: Three main patterns with loadings derived from Principal Component Analysis in women, from the 3C Bordeaux Cohort, 2001 (N=610).

Table S3: Association between the three patterns of polyphenol intake at baseline and the risk of depressive symptomatology over time defined as CES-D score ≥17 for men and ≥23 for women and / or antidepressant treatment, according to the sex, from the 3C Bordeaux cohort, 2001-2017. (N=1,074)

Method S1. Random-effect logistic regression model

Random-effect logistic regression model, also called generalized linear mixed model, is used to analyze the change over time of a binary dependent variable (i.e. with repeated measures), accounting for missing measures over the follow-up period under the missing at random assumption. This model assumes that the relationships between the onset of the event and the covariates differ from one individual to another and takes into account the heterogeneity of the individuals, introduced into the model as random effects (1,2). The random effects represent the correlation between repeated assessments of the dependent variable on the same individual: a first subject-specific random intercept assumes the variability between individuals at inclusion and the random slope assumes variability in the change over time of the dependent variable (1,2). Therefore, random-effect logistic regression model is particularly suitable in the present study focusing on the risk of Depressive Symptomatology (DS), a binary dependent variable repeatedly assessed during the follow-up. Some individuals are more prone to develop DS conditionally to major covariates (variability at inclusion) and in addition, DS is a particular event with a transient nature over time (variability over time). Thus, a random-effect logistic regression model on repeated measures was used including a random intercept and a random slope. In the present study, the choice of one or two random effect was based on model comparison using the Akaike Information Criterion (AIC) to identify the best fitting model.

Results S1. *Patterns of polyphenol intake and risk of depressive symptomatology defined by gender-specific cutoffs (i.e. CES-D score ≥17 for men and ≥23 for women and / or antidepressant treatment)*

Patterns of dietary polyphenol intake in men (**Table S1**)

The Principal Component Analysis (PCA) method identified 3 distinct patterns of dietary polyphenols (PP) in men (Table S1), explaining 45% of the variability of the 21 PP classes consumed by men. As in the main analysis on the study sample without distinction of the gender, the 3 patterns were quantitative scores ranging from 0 to 8 and a higher score indicated a higher adhesion to the PP pattern. The two first components among men (explaining 24.1% and 13.2% of the variability respectively for the 1st and the 2nd principal component) were similar to the main analysis on the whle study sample. The third principal component (explaining 8.1% of the variability) was characterized by low consumptions of hydroxyphenylacetic and hydroxyphenylpropanoic acid and tyrosols, mainly provided by red wine.

Patterns of dietary polyphenol intake in women (**Table S2**)

Regarding women, the PCA identified 3 distinct patterns of dietary PP explaining 44% of the variability of the 21 PP classes consumed by women (score ranging from 0 to 8 for each pattern). The two first principal components in women (explaining 21.2% and 13.4% of the variability for principal component 1 and 2 respectively) were the same as in the study sample without distinction of the gender (Table S2). However, the third principal component on women (explaining 9.4% of the variability) was characterized by high consumptions of theaflavins, monomeric flavanols and flavonols, mainly provided by tea.

Association between 3 patterns of polyphenol intake at baseline and the risk of depressive symptomatology over time according to the sex (**Table S3**)

The risk of DS was examined according to the gender with gender-specific cutoffs (i.e. Center for Epidemiological Studies Depression (CES-D) score ≥17 for men and ≥23 for women and / or antidepressant treatment) (Table S3). Among men, no significant association was observed between the 3 identified patterns of PP intake and the risk of DS after applying polynomial transformation for the second and the third pattern due to non-linearity and adjustment for selected confounders. However, for women, a higher score on the 3rd pattern was associated with a reduced risk of DS after adjustment for selected confounders ($p = 0.014$) and applying a polynomial transformation on this identified 3rd pattern due to non-linearity.

To facilitate the presentation of results from polynomial transformation of the PP patterns in tables, score of 1 was chosen as reference, except for the PP pattern 2 on men, for which a score of 2 was selected as reference due to a small sample of individuals with a score of 1 or fewer (Table S3).

Table S1: *Three main patterns with loadings derived from Principal Component Analysis in men, from the 3C Bordeaux Cohort, 2001 (N=464).*

Polyphenols Pattern 1 **Total Variance : 24.1 %**		**Polyphenols Pattern 2** **Total Variance : 13.2 %**		**Polyphenols Pattern 3** **Total Variance : 8.1 %**	
Polyphenol class	**Loading (%)**	**Polyphenol class**	**Loading (%)**	**Polyphenol class**	**Loading (%)**
Stilbenes	**0.94**	**Hydroxycinnamic Acid**	**0.79**	Dihydrochalcons	0.44
Hydroxy-benzaldehydes	**0.94**	**Alkylmethoxy-phenols**	**0.72**	Monomeric Flavanols	0.43
Dihydroflavonols	**0.94**	**Other polyphenols**	**0.63**	Proanthocyanidins	0.37
Lignans	**0.79**	Flavanones	0.27	Theaflavins	0.35
Tyrosols	**0.68**	Flavones	0.22	Hydroxycinnamic Acid	0.33
Proanthocyanidins	**0.60**	*Chalcons*	-0.12	Alkylmethoxy-phenols	0.31
Anthocyanins	**0.56**	*Flavonols*	-0.13	Other polyphenols	0.25
Hydroxy-phenylacetic/ phenylpropanoic Acid	**0.50**	*Hydroxybenzoic Acid*	*-0.16*	Hydroxybenzoic Acid	0.22
Monomeric Flavanols	0.35	***Monomeric Flavanols***	***-0.70***	*Flavonols*	*-0.10*
Hydroxybenzoic Acid	0.32	***Theaflavins***	***-0.73***	*Alkylphenols*	*-0.16*
Flavonols	0.31			***Tyrosol***	***-0.55***
Hydroxycinnamic Acid	0.16			***Hydroxy-phenylacetic/ phenylpropanoic Acid***	***-0.63***
Other Polyphenols	0.14				
Alkylphenols	*-0.14*				

Table S2 *Three main patterns with loadings derived from Principal Component Analysis in women, from the 3C Bordeaux Cohort, 2001 (N=610).*

Polyphenols Pattern 1 **Total Variance: 21.2 %**		**Polyphenols Pattern 2** **Total Variance: 13.4 %**		**Polyphenols Pattern 3** **Total Variance: 9.4 %**	
Polyphenol class	**Loading (%)**	**Polyphenol class**	**Loading (%)**	**Polyphenol class**	**Loading (%)**
Stilbenes	**0.92**	**Hydroxycinnamic Acid**	**0.79**	**Monomeric Flavanols**	**0.58**
Dihydroflavonols	**0.92**	**Other polyphenols**	**0.70**	**Theaflavins**	**0.58**
Hydroxy-benzaldehydes	**0.91**	**Alkylmethoxy-phenols**	**0.68**	**Flavonols**	**0.51**
Tyrosols	**0.75**	Flavanones	0.16	Other polyphenols	0.45
Lignans	**0.66**	Hydroxy-phenylacetic/ phenylpropanoic Acid	0.13	Alkylmethoxy-phenols	0.45
Hydroxy-phenylacetic/ phenylpropanoic Acid	**0.63**	Chalcons	0.12	Hydroxycinnamic Acid	0.43
Proanthocyanidins	0.45	Tyrosols	0.12	Dihydrochalcons	0.25
Anthocyanins	0.31	Flavones	0.09	Flavones	0.25
Flavonols	0.27	Dihydrochalcons	0.09	Chalcons	0.20
Monomeric Flavanols	0.25	*Anthocyanins*	*-0.10*	Lignans	0.17
Theaflavins	0.15	*Flavonols*	*-0.13*	Proanthocyanidins	0.17
Hydroxycinnamic Acid	0.13	*Isoflavons*	*-0.14*	Hydroxybenzoic Acid	0.15
Alkylmethoxy-phenols	0.13	*Hydroxybenzoic Acid*	*-0.23*	Flavanones	0.10
Other Polyphenols	0.13	*Lignans*	*-0.25*	*Hydroxy-benzaldehydes*	*-0.11*

Polyphenols Pattern 1 **Total Variance: 21.2 %**		**Polyphenols Pattern 2** **Total Variance: 13.4 %**		**Polyphenols Pattern 3** **Total Variance: 9.4 %**	
Polyphenol class	**Loading (%)**	**Polyphenol class**	**Loading (%)**	**Polyphenol class**	**Loading (%)**
Chalcons	0.10	***Monomeric Flavanols***	***-0.70***	*Stilbenes*	*-0.16*
		Theaflavins	***-0.71***	*Dihydroflavonols*	*-0.16*
				Tyrosol	*-0.26*
				Hydroxy-phenylacetic/ phenylpropanoic Acid	*-0.27*

Table S3: *Association between the three patterns of polyphenol intake at baseline and the risk of depressive symptomatology over time defined as CES-D score ≥17 for men and ≥23 for women and / or antidepressant treatment, according to the sex, from the 3C Bordeaux cohort, 2001-2017. (N=1,074)*

	OR [95% CI]*	***p-value****
Men (n=464) :		
- Pattern 1 (for 1 point rise of the score)	0.83 [0.32 ; 2.17)	*0.707*
- Pattern 2 *(polynomial transformation due to non-linearity)*		*0.898*
o Score 1 *vs* 2***	0.01 [0.00 ; 0.37]	
o Score 4 *vs* 2***	1.23 [0.70 ; 2.17]	
o Score 6 *vs* 2***	0.50 [0.21 ; 1.20]	
o Score 8 *vs* 2***	0.20 [0.05 ; 0.83]	
- Pattern 3 *(polynomial transformation due to non-linearity)*		*0.473*
o Score 2 *vs* 1	1.00 [1.00 ; 1.01]	
o Score 4 *vs* 1	0.82 [0.69 ; 0.97]	
o Score 6 *vs* 1	0.51 [0.29 ; 0.89]	
o Score 8 *vs* 1	0.20 [0.05 ; 0.76]	
Women (n=610) :		
- Pattern 1 (for 1 point rise of the score)	1.03 [0.77 ; 1.37]	*0.858*
- Pattern 2 (for 1 point rise of the score)	0.99 [0.70 ; 1.40]	*0.947*
- Pattern 3 *(polynomial transformation due to non-linearity)*		***0.014***
o Score 2 *vs* 1	0.52 [0.37 ; 0.73]	
o Score 4 *vs* 1	0.39 [0.24 ; 0.63]	
o Score 6 *vs* 1	0.36 [0.21 ; 0.61]	
o Score 8 *vs* 1	0.35 [0.20 ; 0.60]	

** Random-effect logistic regression model with a random intercept and a random slope adjusted for age (included in the model time), sex, living condition, educational level, tobacco consumption, daily energy intake, regular physical activity, body mass index and multimorbidity*
*** P-value of the log-likelihood ratio test*
**** Score of 2 as reference due to small sample of individuals with a score of 1 or fewer*

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