BMJ Open

Evaluation of exposure to effervescent drugs in a large health check-up population in France: a cross-sectional study

Germain Perrin,[1,2] Sarah Berdot,[1,2,3] Frédérique Thomas,[4] Bruno Pannier,[4,5] Nicolas Danchin,[4,6] Pierre Durieux,[2,7] Brigitte Sabatier[1,2]

To cite: Perrin G, Berdot S, Thomas F, *et al*. Evaluation of exposure to effervescent drugs in a large health check-up population in France: a cross-sectional study. *BMJ Open* 2018;**8**:e022368. doi:10.1136/bmjopen-2018-022368

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-022368).

Received 15 February 2018
Revised 28 May 2018
Accepted 6 June 2018

For numbered affiliations see end of article.

Correspondence to
Dr Germain Perrin;
germain.perrin@aphp.fr

ABSTRACT

Objectives The relationship between high dietary sodium intake and hypertension is well established. Some drugs are associated with high-sodium content, particularly effervescent tablets (ETs). Despite a possible cardiovascular risk associated with the use of such drugs, observational data describing exposure to ETs in ambulatory subjects are lacking. This study aims to estimate the prevalence of exposure to ETs and to highlight factors associated with this exposure in a large French health check-up population.

Design This was a cross-sectional study.

Setting and participants Participants were French individuals who underwent medical check-ups at the Investigations Préventives et Cliniques centre between April and June 2017.

Results In total, 1043 subjects were included in the study. The prevalence of exposure to ETs in the last 30 days was 26.9% (95% CI 24.2% to 29.6%). Exposure was frequent (ie, two ETs per week or more in the last 30 days) for 7.3% of subjects. Self-medication was the major source of exposure (93.8%). Paracetamol, aspirin, vitamins and betaine accounted for 95.3% of the ETs used. The factors associated with this exposure by multivariate analysis were: male gender, Overseas French origin, depression and body mass index ≥25 kg/m^2. A diagnosis of hypertension or treatment with diuretics were not protective factors against exposure to ETs.

Conclusion Exposure to ETs is frequent in the general population, particularly through self-medication. Clinical conditions associated with low-salt requirements were not associated with lower exposure to ETs, suggesting a lack of awareness by practitioners and patients about this iatrogenic issue.

Strengths and limitations of this study

- To our knowledge, this is the first population-based study that estimates the prevalence and associated factors for exposure to effervescent tablets (ETs).
- The present study includes assessment of exposure to ETs through self-medication, an important information that is not available in databases collecting reimbursement data.
- Possible seasonal variations in exposure to ETs have not been assessed in the present study.
- Due to the single-centre design and the very selected group of subjects, we must be cautious in generalising these results.

INTRODUCTION

Among the variety of risk factors associated with the development and/or worsening of hypertension, high salt intake has been extensively investigated during the last 30 years.[1] Nevertheless, sodium science is still a matter of intense debate, especially concerning the pertinence of drastic low-salt diets for medical conditions such as chronic heart failure[2] and the ability of a low-salt diet to lower cardiovascular outcomes and mortality.[3–5] However, there is a strong consensus in the scientific community concerning the association between a higher risk of hypertension and high dietary salt intake and the impact of a low-salt diet on lowering blood pressure (BP).[6–9] In this context, the WHO recommends limiting daily salt consumption in the general population to 5 g per day, which is equivalent to 2 g of sodium.[10]

High-salt food (particularly cheese, bread and processed food) is recognised as the main source of dietary sodium. However, other potentially important sources are often overlooked, such as pharmaceutical preparations. Indeed, sodium is widely used in drug preparations, both as an active ingredient (for physiological sodium replacement in hydric disorders) and as a cation of an excipient (eg, sodium bicarbonate or sodium citrate used as solubility enhancers or disintegrating agents). Several galenic formulations are associated with high-sodium content, such as effervescent tablets (ETs), intravenous antibiotics or alginates for gastro-oesophageal reflux (GER) symptoms. These high-sodium

containing drugs (HSCDs) could theoretically provoke or worsen cardiovascular conditions, especially hypertension, if taken on a regular basis and/or at a high dose.[11] ETs are generally not indicated for patients who require low-salt or normal salt diets (patients with hypertension and those with congestive heart failure), as non-effervescent alternatives are available.[12] A population-based nested case–control study, published by George *et al*[13] in 2013, showed that patients diagnosed with hypertension or cardiovascular events (non-fatal myocardial infarction, non-fatal stroke or those who died from a vascular cause) were more likely to be prescribed HSCDs. Benitez-Camps *et al* published in 2018 the results of a randomised, cross-over clinical trial, evaluating the effects on BP of exposure to 3 g effervescent paracetamol during a 3-week period in hypertensive subjects. Authors showed that utilisation of effervescent paracetamol in such subjects was associated with a significant increase in 24-hour systolic BP (SBP) measurement (+3.99 mm Hg in the intention-to-treat analysis, and +5.04 mm Hg in the per protocol analysis), compared with a 3-week exposure to non-effervescent paracetamol.[14]

The European Medicines Agency (EMA) published in 2017 a revision of its guideline 'Excipients in the label and package leaflet of medicinal products for human use', including sodium.[15] This revision aimed to offer readily available information to healthcare professionals and patients about the sodium content of drugs, via drug leaflets or packages. Despite this first piece of evidence, little is yet known about the extent of exposure to such HSCDs in the general population, the clinical characteristics of patients who consume HSCDs or the factors associated with exposure to these drugs.

The principal aim of the present study was to evaluate the prevalence of exposure to ETs in a large health check-up population and to explore possible factors associated with such exposure.

METHODS

Study population

The study population was retrieved from a French cohort of volunteers who underwent medical, paramedical and biological examinations between April and June 2017 at the Centre d'Investigations Préventives et Cliniques (IPC) of Paris. This medical centre is subsidised by the French National Healthcare System and proposes all insured and retired individuals (and their families), living in Paris and its suburbs, a free medical examination every 5 years. Impoverished individuals are eligible for a free medical examination every year. The centre conducts approximately 25 000 medical check-ups every year. At the time of administrative registration, subjects were asked whether they were interested in participating in a short educational session on salt consumption. All subjects aged at least 18 years who could understand French and agreed to participate in the study were eligible. After undergoing standardised health examinations and receiving medical counselling, patients were referred to an individual educational session on salt consumption given by a trained pharmacist. For subjects who declined to participate in the study, the information collected was their age, gender and the reason for not participating.

Assessment of outcome (exposure to ETs)

Before the educational session on salt consumption with the pharmacist, the subject completed a specific self-questionnaire. This questionnaire assessed the consumption of ETs, through medical prescription and self-medication. For this study, we identified a drug as 'any substance or combination of substances presented for treating or preventing disease in human beings or animals' (according to the definition given by the European Council Directive 65/65/EEC[16]). All prescribed drugs were considered, regardless of the healthcare professional (medical doctor, dentist and so on). Self-medication was defined as the use of any drug without a medical prescription (this included drugs bought in a community pharmacy or directly taken from the medical cabinet). Once identified, drugs were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System.[17] The frequency of exposure was classified into: 'once a month', 'once a week', 'two or three times per week', 'four to six times per week' and 'once a day or more'. Subjects were defined as unexposed if they did not use any ETs during the last 30 days preceding the medical check-up, occasionally exposed if they reported the use of ETs no more than once a week and frequently exposed if they reported the use of ETs at least twice a week. The sodium content was sought for each effervescent drug identified in the summary of the product characteristics or by contacting the manufacturer when information was missing. The number of tablets consumed during the last 30 days was calculated, allowing the estimation of the daily smoothed drug-associated sodium intake during the last 30 days. To assess the significance of the potential clinical impact of the drug-associated sodium intake estimated this way, we focused on the threshold of 20% of the WHO recommendation, as proposed by the EMA.[18] Possible factors associated with the preference for ETs were investigated using 10-point Likert scales (from 'not important at all to me' for a score of 1 to 'the most important to me' for a score of 10): 'Are you attracted by the taste of ETs?', 'are you attracted by ETs because of their faster action?', 'are you attracted by ETs because they are easier to swallow than classical pills or tablets?' and 'are you attracted by ETs because they are more pleasant to take than other drug formulations?'.

Sample size determination

We estimated that 10% of subjects could be exposed to ETs during a 30-day period, based on the assumption that 20% of subjects self-medicate via the community pharmacy during a 60-day period,[19] and the hypothesis that (1) this proportion may be 40% for medications taken directly by patients from their own medicine cabinet,

resulting in 20% global self-medication during a 30-day period and (2) half of subjects who self-medicate use ETs. The minimum number of subjects required for a 95% CI, with a width of 0.04 (95% CI (8% to 12%)%)), was 864.

Assessment of covariates

In addition to the specific questionnaire, each subject routinely received a complete medical examination, including the recording of anthropometric, biological and environmental parameters. They were also asked to complete a self-administered standardised questionnaire to assess their medical history, environmental exposure, behaviours/lifestyle and psychological status. The following covariates were extracted for analysis: age, gender, body mass index (BMI), SBP and diastolic blood pressure, socioeconomic status, place of birth, comorbidities, depression score, stress score and a score predicting the 10-year risk of cardiovascular death. Standard biological parameters (including blood glucose, lipid profile and renal function) were measured under fasting conditions. Renal function was evaluated with the estimated glomerular filtration rate (EGFR) calculated using the Cockroft-Gault formula. Behavioural covariates extracted were: smoking status (former smoker, current smoker or non-smoker) and number of pack-years, daily alcohol consumption, regular soda consumption, regular physical activity (at least 1 hour of walking per day) and self-medication during the last 30 days. Comedications considered were: antihypertensive drugs, diuretics, corticosteroids and aspirin. Comedications were classified according to the ATC classification.[17] Polymedication was defined as the use of five or more medications per day.[20]

Socioeconomic status was evaluated using the Evaluation de la Précarité et des Inégalités de santé dans les Centre d'Examen de Santé (EPICES) score. This score is a multidimensional estimation of socioeconomic deprivation (social and material deprivation) and ranges from 0 to 100 (a score ≥30 being associated with social deprivation).[21] The level of depression was assessed using the Beck Depression Inventory, which consists of a 0–13-point scale (with the subject considered to be depressed for a score ≥6).[22] Similarly, the level of stress was scored on a 0–16 point scale, according to the four-item Perceived Stress Scale (a higher score being associated with a higher level of stress).[23] The estimation of the 10-year risk of fatal cardiovascular disease was assessed using the Systemic Coronary Risk Estimation (SCORE) chart, calculated using: age, sex, SBP, smoking status, cholesterol level, a history of diabetes, treatment for hypertension and place of birth. A score >5% indicates a high 10-year risk of cardiovascular death.[24] Dietary salt consumption was evaluated using the Exsel score (a tool designed to screen excessive salt consumption among hypertensive patients). It evaluates bread, cheese, processed meats, processed food and processed broth or pilaf consumption and ranges from 0 to 11 (a score ≥5 being associated with excess dietary salt intake in patients with hypertension).[25] For BP assessment, three consecutive measurements were taken by a trained nurse with an electronic device (OMRON705 IT, OMRON Healthcare company, Japan) with the subject in a supine position and 10 min of rest between measurements. The mean of the second and third measurements was used for the analysis.

Hypothesis

We considered the following variables of interest as factors potentially associated with exposure to ETs:

1. Medical conditions associated with low-salt requirement should be associated with a lower exposure to ET (variables: hypertension, BP measurements, treatment with antihypertensive drugs, diuretics or corticosteroids, estimation of kidney function and estimation of the 10-year risk of cardiovascular event).[26–28]
2. Traits associated with a higher salt-sensitivity of blood pressure (ie, subjects who increase their BP with increasing of the salt intake) should be associated with a lower exposure to ETs (variables: age, female gender, BMI, place of birth and given the higher probability of being salt-sensitive among black and Asian individuals[29]).
3. Social deprivation (interpreted as a proxy for socioeconomic status), should be associated with a lower exposure to ET,[19] given the large number of ETs available over the counter (and then which are not reimbursed by social security system) in France (variables: EPICES score and proportion of deprived individuals).
4. Some specific medical conditions could be associated with a preference for effervescent formulation, that is, swallowing difficulties, GER symptoms (given the buffering proprieties of effervescent formulations) and chronic pains.
5. We hypothesised the existence of a craving for salty taste (common with the craving for salty food) and/or a craving for bubbling drinks, associated with preference for ETs (variables: Exsel score and soda consumption).
6. Finally, since effervescent formulations are frequently associated with subjective aspects by patients (ET are sometimes described as pleasant or relaxing), we decided to study variables associated with psychological status (variables: stress level, alcohol and tobacco consumption, perceived health quality and depression).

Ethics

Following the authorisation of the Commission Nationale Informatique et Libertés, the IPC centre performed analyses of data anonymously collected during voluntary health check-ups (each participant is assigned an internal anonymisation number that is used to chain data). All volunteers read and signed the informed consent for the anonymous use of all their recorded variables.

Statistical analysis

The prevalence of exposure to ETs was calculated as the ratio of the number of patients taking at least one ET in the last 30 days to the total number of subjects included

in the study. Data are expressed as the mean±SD for quantitative variables and as numbers and associated percentages for qualitative variables. Group comparisons were performed using the non-parametric Mann-Whitney and Wilcoxon tests for quantitative variables and the χ^2 test for qualitative variables (the Yates correction was used for a theoretical number of observations between three and five, and the Fisher's exact test for numbers under three). We applied Bonferroni's correction to p values to account for multiple comparisons.

Multivariate logistic regression analysis was performed to identify factors associated with exposure to ETs. We performed an imputation for explanatory variables, with no more than 15% missing data, using the Multivariate Imputation by Chained Equations procedure (10 multiple imputations).[30] Explanatory variables significantly associated with outcome (or with a p value <0.2 or highly described to be associated with the outcome in the literature) were included in the initial model. Collinearity issues between explanatory variables and outcome were identified with a variance inflation factor >10.[31 32] A focused principal component analysis was used to identify clusters of explanatory variables with a high level of correlation. In such clusters, variables were rejected to respect the parsimony principle. Interaction terms were identified by integrating all possible interactions in the full model (all significant interactions were taken into account in the final model). We used a backward/forward Akaike stepwise procedure to select the final model. Global goodness of fit of our logistic regression models was evaluated with the Hosmer-Lemeshow test (a p value >0.05 indicating an acceptable goodness of fit). All analyses were performed with R software (V.3.4.3).

Sensitivity analysis

We performed a sensitivity analysis to test the robustness of our results, in which exposed subjects in the logistic regression model were defined as those exposed to at least 1000 mg drug-associated sodium intake in the last 30 days (irrespective of the frequency of exposure). Indeed, a non-negligible proportion of subjects who were exposed to this low level of drug-associated sodium intake (approximately two ETs) could have been exposed at random (eg, ETs provided by a colleague or family member during an acute episode), without their seeking an effervescent formulation. These situations would weaken our statistical model to identify factors associated with exposure to ETs.

Patient and public involvement

Patients were not involved neither in the study design, nor in the conduct of the study. However, in order to disseminate the key messages of this research to study participants, they were informed, only after they completed the questionnaire, about the potential cardiovascular risk associated with exposure to ETs, during an educational session on salt consumption with the pharmacist. Participants were not allowed to modify their responses following this educational session.

RESULTS

Among the 1315 patients screened for participation, 1043 met our inclusion criteria and accepted to participate in the study. The main causes of non-participation were a limited understanding of French (n=66), insufficient time to participate (n=91) and not being concerned by issues associated with salt consumption (n=71). Non-participants did not significantly differ by mean age or sex relative to subjects who agreed to participate (figure 1).

Among the 1043 subjects, 281 declared the use of at least one ET in the last 30 days, leading to a prevalence of use of 26.9% (95% CI 24.2% to 29.6%). In detail, 205 (19.7% (95% CI 17.2% to 22.1%)) were occasionally exposed (ie, no more than one tablet per week) and 76 (7.3% (95% CI 5.7% to 8.9%)) were frequently exposed (ie, two or more tablets per week). These 281 subjects consumed 320 effervescent specialities, with an average of 1.14±0.4 tablets per subject (ranging from 0 to 3). Most of the subjects were exposed through self-medication (93.2%), whereas 5.0% were exposed through medical prescribing. The remaining 1.8% corresponds to subjects exposed to ETs through both self-medication and medical prescribing. Participants who used ET through self-medication had an estimated drug-associated sodium intake of 2.2±2.7 g in the last 30 days. Those participants who used ET in the context of a medical prescribing had an estimated drug associated sodium intake of 11.3±14.5 g ($p<2\times10^{-16}$). Effervescent drugs used in this study were mostly of the alimentary tract and metabolism (A) and nervous system (N) ATC classes (figure 2). For class N (n=197), the most relevant ATC codes were N02BE01 (paracetamol alone; 132/197) and N02BA01 (aspirin alone, 44/197). For class A (n=121), the most representative ATC codes were A16AA06 (betaine; 47/121), A11AA03 (multivitamins with minerals, 31/121) and A11GA01 (ascorbic acid alone; 26/121). Frequently exposed subjects were mostly exposed to class A drugs, particularly vitamins (ascorbic acid alone or multivitamins with or without minerals). These subjects were also frequently exposed to class N drugs, mainly paracetamol. In contrast, occasionally exposed subjects declared more frequent use of class N drugs, again, predominantly paracetamol and aspirin. Other drugs were those occasionally used for gastrointestinal disorders, such as boldine or betaine.

The smoothed estimation of the daily drug-associated sodium intake during the last 30 days was plotted for each exposed subject in light of the WHO recommendations on dietary salt consumption (figure 3). Drug-associated sodium intake was relatively low (below 10% of the WHO recommendations) for most subjects. This corresponded mostly to occasionally exposed subjects. Nevertheless, a non-negligible proportion of subjects were exposed to higher quantities of sodium, above the WHO threshold of 20%, resulting in an increase of global sodium intake

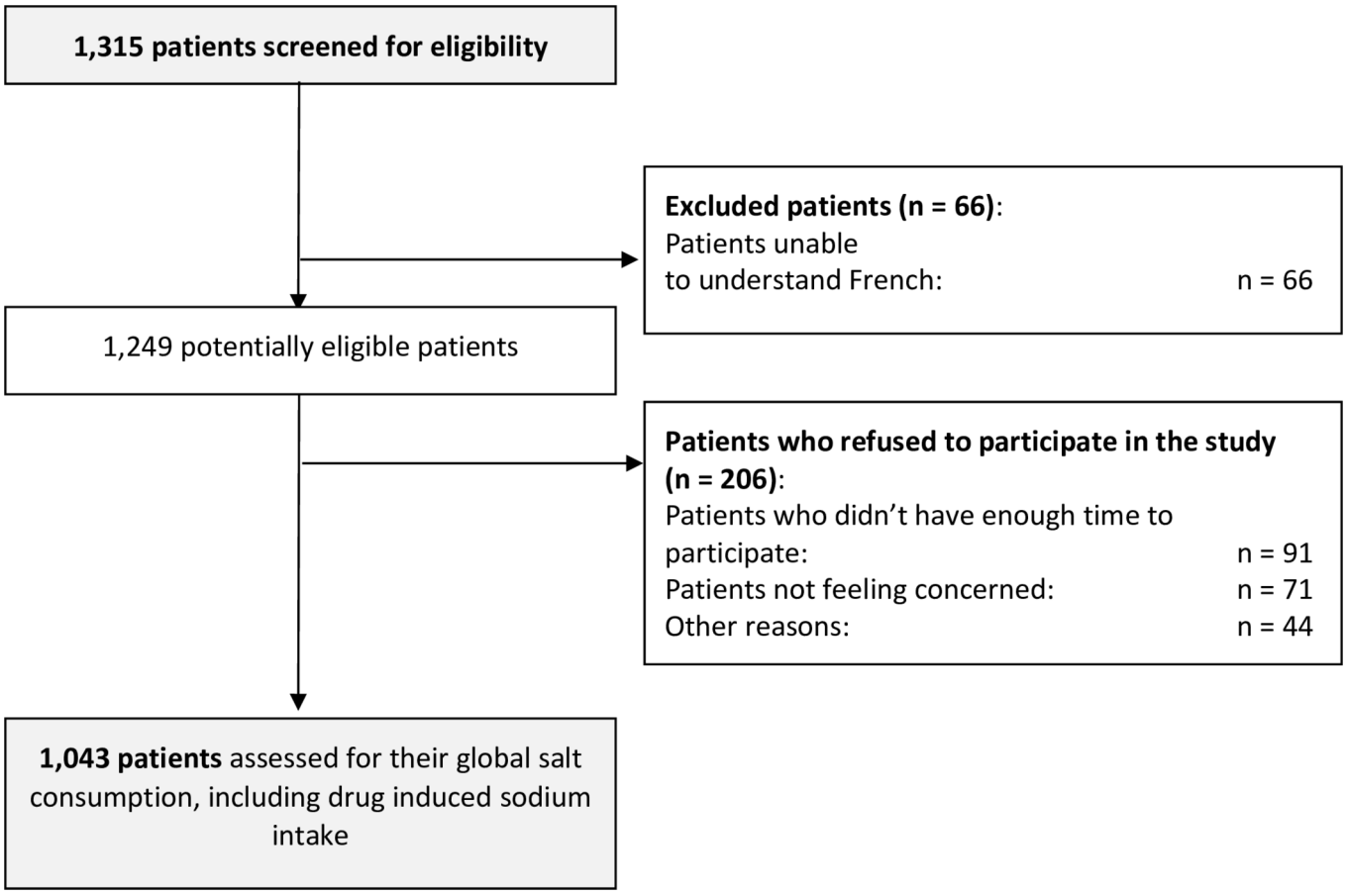

Figure 1 Flow chart of the study.

(60% of these subjects were using paracetamol and 20% aspirin alone).

Patient characteristics are summarised in table 1. Frequently exposed subjects trended towards a higher BMI, were more frequently from Europe (excluding France) or Overseas France, had a higher level of stress, were more depressed and had lower perceived health quality than unexposed subjects. No biological parameter significantly differed between exposure groups, although there was a trend towards higher creatininaemia in the exposed group relative to the unexposed group (reflected by a significantly higher proportion of subjects with EGFR <90 mL/min in the exposed than unexposed group, p=0.02). Smoking status, regular alcohol consumption, regular physical activity and regular soda consumption were not significantly associated with the consumption of ETs. There was no statistical difference between groups for the 10-year risk of cardiovascular death, with a mean SCORE <5% for both groups. As expected, self-medication was strongly and significantly associated with exposure. Among comedications, aspirin and corticosteroid consumption were significantly associated with exposure (expected for aspirin, given the availability of a popular effervescent formulation). The use of antihypertensive drugs and the number of antihypertensive drugs per patient did not significantly differ between exposure groups. The results for all covariables are given in online supplementary resource 1.

We then used the Exsel tool to assess the possibility of a craving for salt to explain the exposure (given the salty taste of ET). The frequency of cheese, bread, processed meats, processed food consumption and processed broth or pilaf use and global Exsel score did not significantly differ between groups (table 2).

Being male and originating from Overseas France were two independent factors significantly associated with exposure to ETs by multivariate analysis (table 3). There was a significant interaction between poor perceived health quality and higher probability of exposure to ETs for subjects who self-medicated. This model included 12 variables for 281 observations (Akaike Information Criterion AIC: 919.7). The p-value for the Hosmer-Lemeshow test was 0.24, indicating an acceptable goodness-of-fit.

In the sensitivity analysis, we found that originating from Overseas France, depression, a BMI >25 kg/m^2 and interaction between poor perceived health quality and self-medication were independent predictive factors associated with exposure to ETs, with the results concordant with those from the main analysis (table 2). The final model for the sensitivity analysis included 12 variables for 140 observations (AIC: 690.5). The p-value for

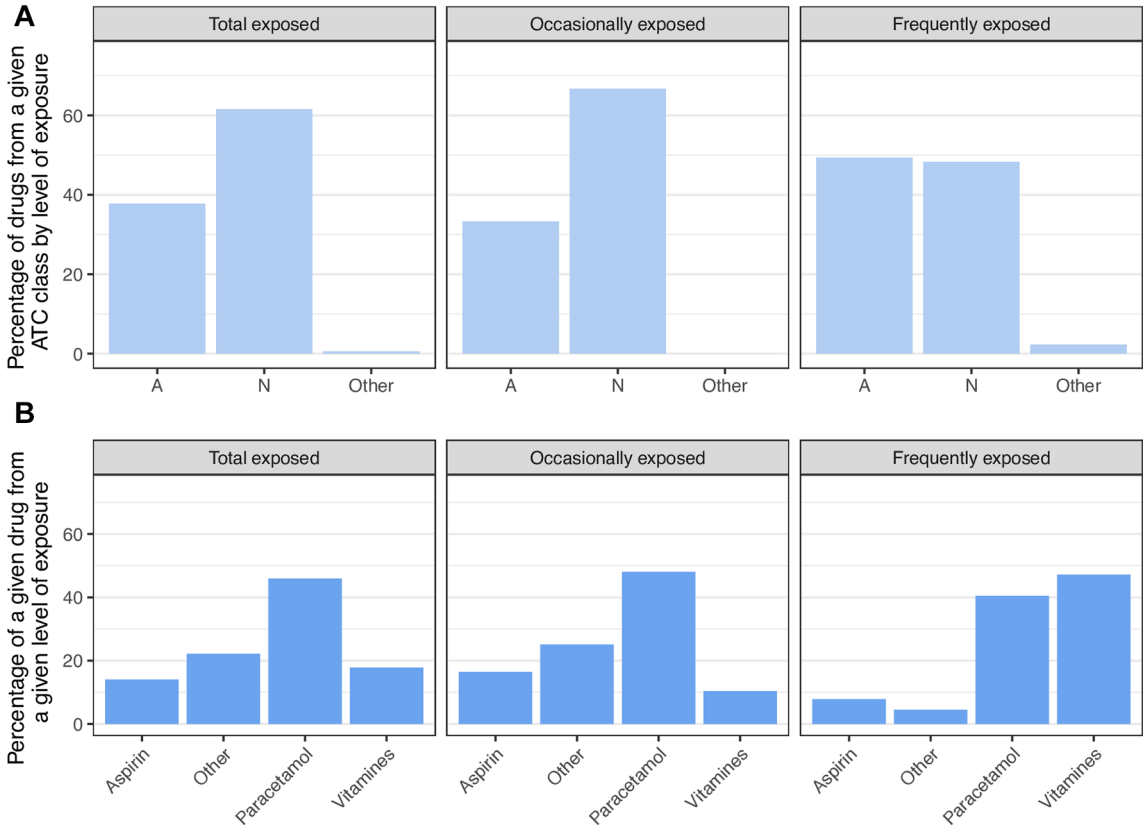

Figure 2 Nature of ET involved in exposure by (A) ATC class and (B) by active ingredient. ATC, Anatomical Therapeutic Chemical; ET, effervescent tablet.

the Hosmer-Lemeshow test was 0.87, again indicating an acceptable goodness of fit.

We finally explored the possible reasons for the preference of patients who declared the use of ETs in the last 30 days for this formulation (figure 4). The main reasons associated with preference for ETs were an impression of faster therapeutic action (mean score: 4.7/10, with no difference between exposure groups) and greater ease in swallowing ETs relative to solid formulations (mean score: 4.6/10, with a trend towards a higher score in the frequently exposed group, p=0.063). Subjects who declared frequent use of ETs had a significantly higher preference for their taste (p=0.0005) and a significantly higher preference for the pleasurable or amusing aspect of ETs (p=0.02).

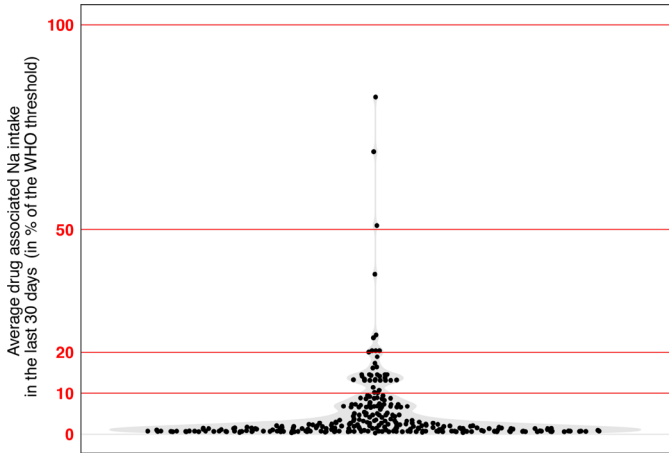

Figure 3 Smoothed estimation of the daily drug-associated sodium intake per day in the last 30 days, expressed as a percentage of the WHO threshold of 2 g sodium per day (one dot=one exposed subjects; n=281).

DISCUSSION

This cross-sectional study shows that exposure to ETs in a large health check-up population is frequent, with 7.3% of subjects declaring the consumption of at least two or three ETs per week in the last 30 days. Self-medication was the main source of exposure in this population, in which subjects exhibited a low level of comorbidity and cardiovascular risk, with vitamin therapy as the principle class involved (ahead of analgesics). This study was performed from April to June. It is possible that exposure to ETs could be subject to seasonal variations, with a large increase during the colder period of the year. This hypothesis, which can be tested by analysing national drug reimbursement data, has important implications, since dietary sodium intake is known to increase during the colder seasons.[33] Finally, the prevalence of comorbidities, usually associated with the choice of effervescent formulations (ie, neurodegenerative disorders, stroke recovery and dysphagia in elderly subjects) was very low, leading to a possible underestimation of the true

Table 1 Baseline characteristics of subjects included in the study

Characteristics	Total (n=1043)	Exposure to ETs in the last 30 days				P value		
		Total exposed (n=281)	Unexposed (n=762)	Occasionally exposed (≤1 ET/30 days) (n=205)	Frequently exposed (≥2–3 ETs/week in the last 30 days) (n=76)	Unexposed versus total exposed	Unexposed versus occasionally exposed	Unexposed versus frequently exposed
Sociodemographic and anthropometric parameters								
Age (years) (mean±SD)	46.2±14.3	45.5±14.1	46.5±14.4	45.8±14.4	44.8±13.1	0.3	0.5	0.3
Female sex (n (%))	414 (39.7)	107 (38.1)	307 (40.3)	77 (37.6)	30 (39.5)	0.5	0.5	0.9
BMI (mean±SD)	25.2±4.4	25.4±4.1	25.2±4.5	25.1±3.8	26.3±4.7	0.1	0.5	0.02*
EPICES score (mean±SD)	24.6±21.8	23.8±21.2	24.9±22.0	22.6±20.3	26.8±23.2	0.5	0.2	0.6
Social deprivation (n (%)) (EPICES score ≥30)	358 (34.3)	87 (31.0)	271 (35.6)	58 (28.3)	29 (38.2)	0.4	0.05	0.7
Place of birth								
France (n (%))	569 (54.6)	142 (50.5)	427 (56.0)	113 (55.1)	29 (38.2)	0.2	1.0	0.003†
Overseas France (n (%))	37 (3.5)	14 (5.0)	23 (3.0)	*8 (3.9)*	4 (5.3)	0.1	0.5	0.04
Africa (n (%))	245 (23.5)	67 (23.8)	67 (23.8)	48 (23.4)	19 (25.0)	0.8	0.9	0.7
Asia (n (%))	45 (4.3)	13 (4.6)	32 (4.2)	*7 (3.4)*	6 (7.9)	0.7	0.6	0.2
Europe excluding France (n (%))	56 (5.4)	18 (6.4)	38 (5.0)	*9 (4.4)*	9 (11.8)	0.3	0.8	0.03*
Comorbidities								
Hypertension (n (%))	118 (11.3)	31 (11.0)	87 (11.4)	19 (9.3)	12 (15.8)	0.9	0.4	0.3
SBP (mm Hg) (mean±SD)	127.7±15.0	127.9±14.6	127.6±15.2	126.7±13.6	130.9±16.7	0.6‡	0.3‡	0.01‡ §
DBP (mm Hg) (mean±SD)	76.0±9.2	75.9±9.2	76.2±9.2	75.6±8.9	77.8±10.1	0.6‡	0.5‡	0.03‡
EGFR <90 mL/min (n (%))	249 (23.9)	53 (18.9)	196 (25.7)	37 (18.0)	16 (21.1)	0.02*	0.02*	0.4
Swallowing difficulties (n (%))	25 (2.5)	7 (2.6)	18 (2.4)	5 (2.5)	2 (2.7)	0.9	1.0	0.7
Stress score (mean±SD)	4.7±3.1	5.3±3.3	4.5±3.0	4.9±3.2	6.2±3.3	0.002†	0.2	8.0×10^{-5}¶
Depression score (mean±SD)	1.8±2.9	2.3±3.1	1.6±2.7	*1.9±2.7*	3.6±4.3	0.009§	0.1	0.005*
Depression (n (%)) (depression score ≥6)	95 (11.3)	37 (16.6)	58 (9.4)	*19 (11.7)*	18 (29.5)	0.004§	0.4	2.0×10^{-06}¶
Perceived health quality (mean±SD)	7.2±1.7	7.0±1.7	7.2±1.6	7.1±1.5	6.6±2.0	0.1	0.5	0.02*
GER symptoms (n (%))	273 (26.8)	88 (32.1)	184 (24.9)	*62 (31.3)*	26 (34.2)	0.02*	0.07	0.08
Sciatica (n (%))	238 (23.6)	64 (24.1)	174 (23.4)	43 (22.2)	21 (29.2)	0.8	0.7	0.3
Osteoarticular pain (n (%))	416 (40.7)	118 (42.8)	298 (39.9)	83 (41.1)	35 (47.3)	0.4	0.8	0.2
SCORE (mean±SD)	1.35±1.5	1.36±1.5	1.35±1.5	1.45±1.3	1.03±1.0	0.7	0.3	0.3
Comedications								
Self-medication in the last 30 days (n (%))	607 (58.2)	270 (96.1)	337 (44.2)	201 (98)	69 (90.8)	2.2×10^{-16}¶	2.0×10^{-16}¶	1.0×10^{-14}¶
Total number of drug per day (mean±SD)	0.51±1.18	0.47±1.07	0.52±1.21	0.49±1.10	0.42±1.01	0.7	0.8	0.6
≥5 drugs per day, defining polymedication (n (%))	20 (1.9)	3 (1.1)	17 (2.2)	2 (1.0)	1 (1.3)	0.3	0.4	1
Antihypertensive drugs (n (%))	96 (9.2)	25 (8.9)	71 (9.3)	19 (9.3)	7 (9.2)	0.2	0.1	0.9

Continued

Table 1 Continued

Characteristics	Total (n=1043)	Exposure to ETs in the last 30 days				P value		
		Total exposed (n=281)	Unexposed (n=762)	Occasionally exposed (≤1 ET/30 days) (n=205)	Frequently exposed (≥2–3 ETs/week in the last 30 days) (n=76)	Unexposed versus total exposed	Unexposed versus occasionally exposed	Unexposed versus frequently exposed
Hypertensive subjects taking more than one antihypertensive drug (n (%))	47 (39.8)	12 (38.7)	35 (40.2)	7 (36.8)	5 (41.6)	0.8	0.9	1.0
Diuretics, any indication (n (%))	52 (5.0)	17 (6.0)	35 (4.6)	10 (4.9)	7 (9.2)	0.4	0.9	0.1
Corticosteroids (n (%))	27 (2.6)	13 (4.6)	14 (1.8)	8 (3.9)	5 (6.6)	0.01§	0.1	0.02*
Aspirin (n (%))	124 (11.9)	53 (18.9)	71 (9.3)	36 (17.6)	17 (22.4)	8.0×10^{-5}¶	0.003†	0.0005†

* p-value < 0.033, † p-value < 0.003, ‡ Adjusted for age and sex, § p-value < 0.017, ¶ p-value < 0.0003 (Bonferroni correction).
BMI, body mass index; DBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; ET, effervescent tablet; GER, gastro-oesophageal reflux; SCORE, Systemic Coronary Risk Estimation (calculated for subjects aged 40–65 years); SBP, systolic blood pressure.

Table 2 Estimation of dietary sodium intake in subjects included in the study

Characteristics	Total (n=1043)	Exposure to ET in the last 30 days				P values		
		Total exposed (n=281)	Unexposed (n=762)	Occasionally exposed (≤1 ET/30 days) (n=205)	Frequently exposed (≥2–3 ETs/week in the last 30 days) (n=76)	Unexposed versus total exposed	Unexposed versus occasionally exposed	Unexposed versus frequently exposed
Dietary salt consumption								
Cheese at least one time per day (n (%))	387 (37.1)	105 (37.4)	282 (37.0)	78 (38.0)	27 (35.5)	0.9	0.8	0.8
Bread: 0–3 pieces per day (n (%))	645 (61.8)	173 (61.6)	472 (61.9)	123 (60.0)	50 (65.8)	0.6	0.7	0.6
Bread: four or five pieces per day (n (%))	264 (25.3)	71 (25.3)	193 (25.3)	54 (26.3)	17 (22.4)	0.6	0.4	0.6
Bread: six pieces or more per day (n (%))	134 (12.8)	37 (13.2)	97 (12.7)	28 (13.7)	9 (11.8)	0.9	0.6	0.2
Processed meat at least two times per week (n (%))	346 (33.2)	97 (34.5)	249 (32.7)	68 (33.2)	29 (38.2)	0.6	0.9	0.3
Processed food at least two times per week (n (%))	519 (49.8)	140 (49.8)	379 (49.7)	103 (50.2)	37 (48.7)	1.0	0.9	0.9
Use of processed broth or pilaf(n (%))	575 (55.1)	154 (54.8)	421 (55.2)	114 (55.6)	40 (52.6)	0.9	0.9	0.7
Exsel score (mean±SD)	3.8±2.1	3.9±2.0	3.8±2.1	3.9±2.0	4.0±2.0	0.3	0.5	0.4

ET, effervescent tablet.

Table 3 Results for multivariate analysis

Variable	Model 1* *(main analysis)*	Model 2† *(sensitivity analysis)*
Gender: male	*AOR: 1.64 (95% CI 1.18 to 2.30)*	*AOR: 1.42 (95% CI 0.96 to 2.14)*
Origin: France	*Reference*	*Reference*
Origin: Overseas France	*AOR: 5.45 (95% CI 2.21 to 14.17)*	*AOR: 5.79 (95% CI 2.39 to 13.84)*
Depression	*Not in the final model*	*AOR: 2.23 (95% CI 1.31 to 3.76)*
BMI >25 kg/m^2	*Not in the final model*	*AOR: 1.05 (95% CI 1.01 to 1.10)*
Interaction between poor perceived health quality and self-medication	*AOR: 1.54 (95% CI 1.10 to 2.11)*	*AOR: 1.59 (95% CI 1.12 to 2.27)*

Significant p values are in italicised characters.
*Adjusted for: origin, stress level, gender and perceived health quality and self-medication.
†Adjusted for: origin, gender, depression, perceived health quality, depression, BMI and self-medication.
AOR, adjusted OR; BMI, body mass index; GOF, goodness of fit.

prevalence in a more general outpatient setting population (such subjects with high comorbidity level are classically not referred to preventive centres).

In bivariate analysis, we found that exposed subjects were more likely to come from Overseas France, have a higher level of stress (recognised as a possible cardiovascular risk factor[34]), be more depressed and to have a lower perceived health quality. We also observed a trend towards a higher prevalence of GER symptoms in exposed subjects, with a dose–response relationship. This may be explained by the large quantity of bicarbonate generally found in effervescent formulations, which can buffer stomach acidity and help to reduce symptoms. Frequently exposed subjects had a tendency to have a higher BMI, which is a typical preventable cardiovascular risk factor. In multivariate analysis, male gender, origin of the subject and a high depression score were the only independent predictive factors for exposure to ETs. Participants with Overseas France origin are very likely to be black subjects (in our study sample, most participants of them were from West Indies, Martinique and Guadeloupe). This point is of interest, since black subjects are a population characterised by a high prevalence of salt-sensitive blood pressure.[29]

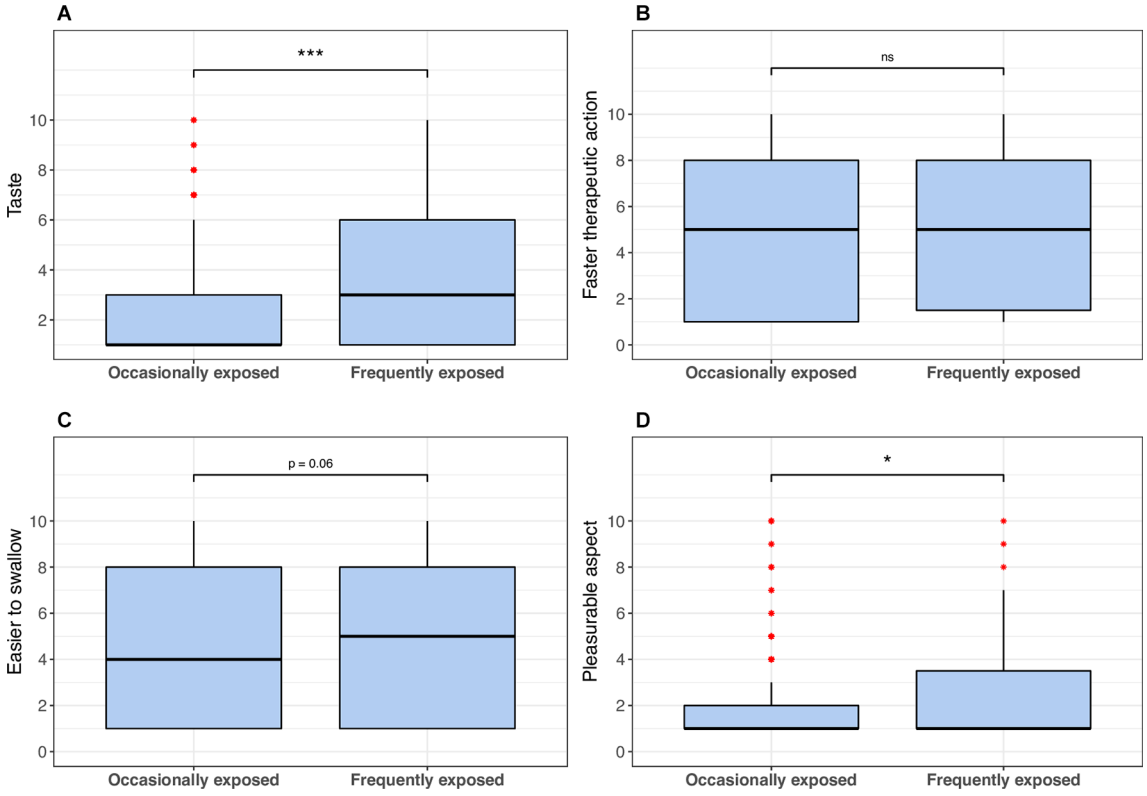

Figure 4 Reasons associated with the preference for ETs in exposed subjects. (A) taste, (B) feeling of faster therapeutic action, (C) easier to swallow and (D) pleasurable aspect. Y-axis gives the Likert score (ranging from 1 to 10). Red dots represent outliers. *P<0.05, ***p<0.001. ns, non-significant.

Of note, a diagnosis of hypertension was not a protective factor against ET exposure, despite existing national guidelines recommending that patients with hypertension do not use effervescent medications.[26–28] Similarly, treatment with diuretics did not appear to be a protective factor, although excess sodium intake has been associated with a loss of efficacy of cardiovascular drugs, including diuretics.[35] This suggests that this possible iatrogenic issue is not taken into account by patients, possibly due to a lack of information provided by practitioners or pharmacists at the time of prescribing and/or dispensing. However, it is difficult to draw any conclusion concerning this issue given the broad range of ETs used for self-medication in the present study (including medications taken from the medicine cabinet without any medical or pharmaceutical supervision). In our study, social deprivation was not a protective factor against exposure to ETs, as exposure was mostly by self-medication. This can also be explained by the definition of self-medication used: impoverished individuals can benefit from reimbursement of their prescribed medications, making ETs widely available via their medicine cabinet throughout the year.

Drug-associated sodium intake was relatively low (ie, less than 10% of the WHO's recommendations for dietary sodium intake) for most subjects. However, a non-negligible proportion of subjects were exposed to more than 20% of this threshold, leading to a significant increase in global sodium intake. In addition, although most subjects were exposed to low quantities of sodium associated with ET use, the existence a large pool of patients who regularly consume ETs is of importance because the consumption of ETs can substantially increase during an acute medical episode (eg, osteoarticular pain, sciatica or infections associated with the cold season) and because such subjects could be more likely to use ET in a daily basis while developing chronic conditions. Such a sudden increase of sodium intake may be associated with the decompensation of cardiovascular conditions, such as congestive heart failure, for which perturbations in sodium levels could constitute a pathophysiological trigger.[36] The observed association between high level of exposure and high level of SBP (after adjustment for age and sex, see table 1) should be interpreted cautiously (1) because of the cross-sectional design of the study and (2) because a possible indication bias could not be excluded (patients taking medications are more likely to suffer from illness associated with increased blood pressure).

Finally, the main reasons explaining the preference for ETs (although non-effervescent alternatives are available) were an impression of a faster therapeutic effect and ease in swallowing the medicine relative to solid formulations. Frequently exposed subjects significantly differed from occasionally exposed subject by their preference for the taste and the pleasurable aspect of effervescent formulations. This suggests that there are two relatively distinct populations of ET users: frequent users and occasional users, who have distinct profiles (this is supported by the differences observed between the two multivariate models). Altogether, these results provide a window of opportunity for improving medical and pharmaceutical counselling, as alternative formulations with low sodium content (such as orodispersible, oral suspension or oral granule formulations) can be proposed for their practical aspects, for example, to patients with dysphagia for whom they are well-suited.

The Exsel tool[25] was integrated in our questionnaire to assess a possible craving for salt associated with the preference for ETs (given their salty taste). Our results did not support the existence of such behaviour, since there were no differences in consumption of food with high levels of hidden salt or added salt (processed broth or pilaf) between the various exposure groups. We acknowledge that this food frequency questionnaire constitutes a screening tool for salt consumption and stronger conclusions should be derived from 24 hours urine sodium measurements.

The principal limitation of this study is its lack of generalisability, since it was conducted in a health check-up population with an unbalanced proportion of men and impoverished individuals. Aside from these aspects, subjects who did not accept to participate in the study did not significantly differ by age or sex, and the main cause of refusal was the lack of time to participate (the full medical examination lasted more than 2 hours). In contrast, the strengths of this study included: (1) the use of multidimensional scores to estimate variables, particularly subjective aspects such as depression, social deprivation, level of stress and dietary salt consumption and (2) the fact that all variables related to the primary objective (ie, evaluation of the exposure to ET) were collected by a single trained pharmacist during an educational session, resulting in no missing data for these variables.

In conclusion, exposure to ETs is frequent in a health check-up population, particularly through self-medication. Clinical conditions associated with a required low-salt intake (ie, hypertensive subjects and patients treated with a diuretic) were not associated with lower exposure to ETs, despite the existence of a myriad of therapeutic alternatives (such as orodispersible drugs or liquid formulations). Thus, an effort should be made by health professionals to inform high-risk patients about this potential iatrogenic risk. Further studies are required to characterise this exposure in high-risk populations, such as elderly or hospitalised patients.

Author affiliations
[1]Department of Pharmacy, Georges-Pompidou European Hospital, Paris, France
[2]INSERM UMR 1138 Team 22: Information Sciences to Support Personalized Medicine, Cordelier Research Center, Paris, France
[3]Department of Clinical Pharmacy, EA4123, Paris-Sud University, Châtenay-Malabry, France
[4]Centre d'Investigations Préventives et Cliniques, Paris, France
[5]Department of Cardiology, Manhès Hospital, Fleury-Merogis, France
[6]Department of Cardiology, Georges Pompidou European Hospital, Paris, France
[7]Department of Biomedical Informatics and Public Health, Georges-Pompidou European Hospital, Paris, France

Acknowledgements Authors would like to acknowledge Dr Sebastian Lequime for his support in generating figures. No sources of funding were used to conduct this study or prepare this manuscript.

Contributors All authors were involved in the conception and design of this study. GP and FT were responsible for collecting the data and for conducting analyses. GP, SB, FT, PD and BS were responsible for interpreting the results and drafting the manuscript. GP, SB, FT, ND, PD and BS critically revised the manuscript. All authors have read and approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer GP affirms that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted. Any discrepancies from the study as planned have been explained.

Competing interests None declared.

Patient consent Not required.

Ethics approval Following the authorisation of the Commission Nationale Informatique et Libertés (CNIL), the IPC center performed analyses of data anonymously collected during voluntary health check-ups. All volunteers read and signed the informed consent for the anonymous use of all their recorded variables.

Data sharing statement Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.7h41b81

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