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BMJ Open Involvement of common risk factors in the associations between lifetime unemployment exposure, major health outcomes and mortality: a retrospective and prospective study in a large population-based French cohort

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ABSTRACT

Objectives Uncertainty exists as to what extent common risk factors are involved in the associations of unemployment with major health outcomes and mortality.

Design A retrospective and prospective observational study.

Setting A large population-based French cohort (CONSTANCES).

Participants 99 430 adults at baseline who have been exposed to unemployment during their lifetime and 54 679 of them who were followed for 7 years after baseline.

Primary outcome measures Testing the mediating roles of several risk factors at baseline in the associations of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates during a 7-year follow-up. Direct and indirect effects were calculated for each risk factor and all together using logistic regression models adjusted for major confounders including sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions.

Results Estimates (95% CIs) of the direct and indirect effects for smoking are 0.0083 (0.0044 to 0.0122), $p<0.0001$ and 0.0010 (0.0007 to 0.0014), $p<0.0001$ on cardiovascular disease rate; 0.0059 (0.0028 to 0.0089), $p=0.0002$ and 0.0007 (0.0004 to 0.0010), $p<0.0001$ on cancer rate; 0.0105 (0.0058 to 0.0151), $p<0.0001$ and 0.0010 (0.0005 to 0.0014), $p<0.0001$ on all-cause mortality. The figures for alcohol consumption are, respectively, 0.0076 (0.0034 to 0.0118), $p=0.0004$ and 0.0004 (0.0002 to 0.0005), $p=0.0006$; 0.0067 (0.0035 to 0.0100), $p<0.0001$ and 0.0004 (0.0002 to 0.0005), $p<0.0001$; 0.0114 (0.0064 to 0.0164), $p<0.0001$ and 0.0004 (0.0001 to 0.0006), $p=0.0009$. For depressive symptoms, 0.0084 (0.0040 to 0.0128), $p=0.0002$ and 0.0007 (0.0002 to 0.0011), $p=0.005$; 0.0053 (0.0017 to 0.0089), $p=0.004$ and 0.0001 (–0.0002 to 0.0005), $p=0.51$; 0.0088 (0.0031 to 0.0144), $p=0.002$ and 0.0010 (0.0004 to 0.0015), $p=0.0005$. For leisure-time physical inactivity, 0.0083 (0.0044 to 0.0122), $p<0.0001$ and 0.0003 (0.0001 to 0.0005), $p=0.0006$; 0.0057

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study analysed recent data collected from a large population-based cohort.
- ⇒ Data were robust, based on administrative sources for the assessment of lifetime unemployment exposure and on clinical sources for diagnoses of risk factors, cardiovascular diseases, cancers and mortality.
- ⇒ Associations between lifetime unemployment exposure, the prevalence of risk factors at baseline and the rates of cardiovascular diseases, cancers and deaths during follow-up were assessed while adjusting for major confounders.
- ⇒ As the cohort was not representative of the general population, the external validity of the findings is not warranted.
- ⇒ Despite the large population size, the lack of statistical power precluded the assessment of specific types of cardiovascular diseases and cancers as well as the causes of death.

(0.0026 to 0.0088), $p=0.0004$ and 0.0002 (0.0001 to 0.0003), $p=0.002$; 0.0105 (0.0058 to 0.0152), $p<0.0001$ and 0.0004 (0.0002 to 0.0007), $p<0.0001$. For blood triglycerides, 0.0080 (0.0042 to 0.0119), $p<0.0001$ and 0.0005 (0.0004 to 0.0007), $p<0.0001$; 0.0057 (0.0026 to 0.0087), $p=0.0003$ and 0.0001 (–0.0001 to 0.0002), $p=0.32$; 0.0103 (0.0057 to 0.0149), $p<0.0001$ and 0.0002 (0.0000 to 0.0004), $p=0.06$. The figures for all risk factors when tested together were 0.0075 (0.0022 to 0.0128), $p=0.005$ and 0.0020 (0.0011 to 0.0027), $p<0.0001$; 0.0052 (0.0011 to 0.0093), $p=0.01$ and 0.015 (0.0009 to 0.0020), $p<0.0001$; 0.0102 (0.0035 to 0.0169), $p=0.003$ and 0.0022 (0.0011 to 0.0031), $p<0.0001$.

Conclusions These analyses show that common risk factors such as smoking, alcohol consumption, depressive symptoms, leisure-time physical inactivity and blood triglycerides mediate up to 10% of the associations of



lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates when tested separately and approximately 20% when tested all together. This highlights the existence of other major mediating pathways that have yet to be identified.

INTRODUCTION

Unemployment is associated with a high prevalence and incidence of cardiovascular diseases^{1–6} and cancers,¹⁷ possibly translating into premature mortality.^{8,9} In the hypothesis where these links are causal, the underlying pathological pathways remain unclear. One obvious possibility is that unemployment may favour the occurrence of unhealthy behaviours and other risk factors. Indeed, unemployment is associated with an increased prevalence and incidence of smoking, non-moderate alcohol consumption, leisure-time physical inactivity, unbalanced diet as well as obesity, hypertension, diabetes, sleep disorders and depression.^{10–17} These are well-known risk factors that could mediate in part the observed association of unemployment with the prevalence and incidence of cardiovascular diseases and cancers.

Testing this possibility requires taking into account the fact that unemployment is strongly interrelated with both social position and working conditions,¹⁸ which are powerful determinants of health and mortality.^{19–20} Thus, individuals with a low social position, as measured by educational level, occupational class or income, have higher risks of cardiovascular diseases^{21–22} and cancers^{23–24} that could be related to overexposure to risk factors such as smoking, non-moderate alcohol consumption, leisure-time physical inactivity, obesity, diabetes, hypertension, dyslipidaemia, sleep disorders and depression.^{25–31} Likewise, individuals with bad working conditions have increased risks of cardiovascular diseases³² and cancers³³ possibly because they are overexposed to smoking, non-moderate alcohol consumption, leisure-time physical inactivity, obesity, hypertension, diabetes, sleep disorders and depression.^{34–41}

The aim of the present study is to explore the extent to which these risk factors have a mediating role in the association of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates in a large population-based cohort.

METHODS

Study population

205 203 adults aged 18–75 years and affiliated with the general health insurance system, which covers 85% of the French population, were enrolled in the CONSTANCES cohort between January 2012 and December 2020 using a random sampling scheme stratified on sex, age, socioeconomic status and region.⁴² The inclusion rate was 7.3% with criteria comprising the obligation to provide written informed consent, to undergo a comprehensive health examination in one of the twenty-one participating medical centres scattered across the metropolitan territory and to complete questionnaires on

lifestyle, health-related behaviours, social and occupational conditions.

The prevalence of risk factors at baseline was analysed in participants who were exposed to unemployment during their lifetime (n=99 430). Cardiovascular disease, cancer and mortality rates were analysed in a subset of these participants (n=54 679) who could be followed for 7 years after baseline (online supplemental figure 1).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Lifetime exposure to unemployment

Unemployment exposure of participants during their lifetime was documented by a questionnaire in which they were asked to report each time they had stopped working for a period of more than 6 months and why (unemployment, health issue, pregnancy or parental leave). Only participants who gave unemployment as the reason and not health issue, pregnancy or parental leave were considered unemployed. The existence of unemployment episodes was confirmed by administrative data from the French national pension system which also provided the total number of unemployed quarters for each participant. The analyses were ultimately based on the number of unemployed quarters that could not be entirely captured by self-reporting of 6-month unemployment episodes and when some discrepancy was present, that is, when participants declared no unemployment episodes but had recorded unemployed quarters. Note that the existence of a recorded unemployed quarter in the French national pension system did not mean that people were unemployed for 3 months; the whole quarter was validated as soon as people did not work for 50 separate or consecutive days. Note also that unemployed periods occurring before the first job were not captured by self-reporting of 6-month unemployment episodes or by the administrative recording of unemployed quarters. The distribution of unemployed quarters in participants who were exposed to unemployment during their lifetime is reported in online supplemental figure 2.

Social position and working conditions at baseline

The social position of participants was characterised by several indicators including education, occupation, income, spouse's occupation and social vulnerability. The distributions of these indicators are shown in online supplemental table 1. Educational attainment was classified into four levels depending on the number of years of study: ≤11, 12–13, 14–16 or ≥17. Occupation of participants and spouses was reduced from a 10-level classification in the original inquiry to three grades: blue collar/clerk, intermediate and management. Income that included monthly earnings of all household members was ranked as low (below €1500), middle (between €1500 and €2800), high (between €2800 and €4200) or very high

(above €4200). These arbitrary thresholds were dictated by the inquiry that included seven levels of income and the need to balance the number of participants between groups. Social vulnerability was evaluated by the EPICES score, based on a questionnaire comprising 11 binary items exploring material and social deprivation,⁴³ that was categorised into terciles (low, intermediate or high social vulnerability) for the analyses. Given that these different indicators assessed complementary and interdependent aspects of social position, a global score was calculated by giving each indicator a value of 1 to the least privileged group, 2 or 3 to intermediary groups and 3 or 4 to the most privileged group depending on whether the indicator encompassed 3 or 4 levels, by summing the values and by dividing the sum by the number of available indicators for each participant. This global score was categorised into terciles (low, middle or high social position) as previously reported.⁴⁴

Working conditions of participants were assessed by a total of 19 occupational exposures whose distributions are shown in online supplemental table 2. These included a series of organisational, physical, biomechanical, chemical and psychosocial factors: commuting time, clocking in and out, regular working hours (on daily and weekly basis), long working hours (over 10 hours per week day), night work, dealing with the public, driving on public road, repetitive work (imposed by a machine, a procedure or someone), working with a screen, standing work posture, handling heavy loads (over one kilogram), physically demanding work, exposure to vibrations, exposure to noise, outdoor work, working in the cold, working in the heat, exposure to chemicals and the scale assessing effort–reward imbalance of work that was divided into terciles (low, average or high imbalance).⁴⁵ As these occupational exposures were significantly interrelated with each other, working conditions were considered as a whole, which is reality for workers who are not facing only one or a few exposures. Thus, all exposures were combined into a global score that was calculated by giving to each exposure a value of 1 to the least exposed group, 3 to the more exposed group and 2 to intermediary groups whenever the exposure encompassed 3 levels, by summing the values and by dividing the sum by the number of available exposures for each participant. This global score was categorised into terciles (bad, average or good working conditions) as previously described.⁴⁴

Risk factors at baseline

Besides non-modifiable risk factors that included sex, age divided into terciles (18–39, 40–54, 55–75 years old) and parental histories of cardiovascular disease and cancer (coded as binary variables (Y/N)), several behavioural and clinical factors were considered and coded as binary variables to estimate their prevalence at baseline. Behavioural factors included smoking, non-moderate alcohol consumption (>3 drinks/day in men, >2 drinks/day in women) and leisure-time physical inactivity. Leisure-time physical inactivity assessment was based on a three-item questionnaire

inquiring about regular practice of walking, cycling or other sports, gardening and housekeeping over the past 12 months; each item was noted 0 if the answer was no, 1 if the practice was regular but low (less than 2 hours per week), 2 if the practice was regular and higher; the score calculated by summing the items which ranged from 0 (not active at all) to 6 (very active) was used to characterise leisure-time physical inactivity (participants with a score <2). Clinical factors included obesity, hypertension, dyslipidaemia, diabetes, sleep disorders and depressive symptoms. These factors were assessed during the visit in the medical centres using standardised procedures in order to guarantee high-quality data.⁴⁶ Participants were instructed to fast before the visit that took place between 8:00 and 10:00 hours, ensuring a fasting period of at least 8 hours. Height and weight were measured for the calculation of body mass index and the diagnosis of obesity (body mass index ≥ 30 kg/m²). Blood was collected to determine concentrations of glucose, total cholesterol and triglycerides. Diabetes was diagnosed by fasting glycaemia ≥ 7 mmol/L and/or antidiabetic drug (Anatomical Therapeutic Chemical (ATC) code A10) use while dyslipidaemia was characterised by hypercholesterolaemia (≥ 6.5 mmol/L) and/or hypertriglyceridaemia (≥ 2.2 mmol/L) and/or lipid-lowering drug (ATC code C10) use. Systolic and diastolic blood pressures were measured twice in sitting position on each arm at 2 min interval after 5 min of rest using an automated sphygmomanometer. The arm giving the highest values was considered as the reference arm on which a third measure was taken after one additional minute of rest. The average of the three measurements was used for the analyses. Hypertension was diagnosed if systolic blood pressure was ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or antihypertensive drugs (ATC codes C02, C03, C07, C08, C09) were taken. Depressive symptoms were assessed using the Centre of Epidemiologic Studies Depression (CESD) scale and defined by a score ≥ 19 in both sexes. Sleep disorders were based on the repetitive occurrence of multiple wake-ups at night and/or fatigue after normal wake-up and/or sleep duration too short (<5 hours 30 min) or too long (>8 hours 30 min). When a clinical risk factor was diagnosed, physicians systematically inquired about the age at which the risk factor was first detected during lifetime.

Risk factors at baseline were also analysed as numeric variables, whose distributions are reported in online supplemental figure 3, in order to assess their mediating role in the associations of lifetime unemployment exposure with cardiovascular, cancer and mortality rates during follow-up. Smoking was expressed by the habitual number of items (cigarettes, cigarillos, cigars, pipes) smoked per day, alcohol consumption by the habitual number of drinks consumed per day, leisure-time physical inactivity by the score ranging from 0 to 6 as described above, dyslipidaemia and diabetes by blood cholesterol, triglyceride and glucose levels measured during the medical visit, sleep disorders by sleep duration and depressive symptoms by the CESD score.

Cardiovascular disease, cancer and mortality rates during follow-up

Information on the occurrence of cardiovascular diseases, cancers and deaths during follow-up was obtained from the French administrative healthcare database that contains data on all French patients having long-term chronic diseases with the date of diagnosis, hospital stays with dates of entry and exit, diagnoses, death during hospitalisation and its causes. The most common types of cardiovascular diseases (stroke, coronary heart disease, peripheral arterial disease) were retained for the analyses and coded globally as a single binary variable (Y/N) combining the occurrence of any of the three diseases. Stroke was defined by the diagnosis of acute events (subarachnoid haemorrhage (International Classification of Disease-10 code, I60), intracerebral haemorrhage (I61), other non-traumatic intracranial haemorrhage (I62), cerebral infarction (I63), stroke not specified as haemorrhage or infarction (I64)) and/or chronic conditions related to strokes that occurred during follow-up (other cerebrovascular diseases (I67), cerebrovascular disorders in diseases classified elsewhere (I68), sequelae of cerebrovascular disease (I69), hemiplegia (G81)). Coronary heart disease was also defined by the diagnosis of acute events (angina pectoris (I20), acute myocardial infarction (I21), subsequent myocardial infarction (I22), current complications following acute myocardial infarction (I23), other acute ischaemic heart diseases (I24)) and/or chronic conditions related to coronary heart diseases that occurred during follow-up (chronic ischaemic heart disease (I25)). Peripheral arterial disease was characterised by the diagnosis of atherosclerosis (I70), other peripheral vascular diseases (I73) or arterial embolism and thrombosis (I74).

The most common types of cancers (breast, skin, prostate, cervical, thyroid, colon, lung and ovarian) were considered for the analyses and coded globally as a single binary variable (Y/N) combining the occurrence of any of these cancers. Breast cancer was defined by the diagnosis of malignant neoplasm of breast (C50), skin cancer by the diagnosis of melanoma (C43) or other malignant neoplasms of skin (C44), prostate cancer by the diagnosis of malignant neoplasm of prostate (C61), cervical cancer by the diagnosis of malignant neoplasm of cervix uteri (C53), thyroid cancer by the diagnosis of malignant neoplasm of thyroid gland (C73), colon cancer by the diagnosis of malignant neoplasm of colon (C18), recto-sigmoid junction (C19) or rectum (C20), lung cancer by the diagnosis of malignant neoplasm of trachea (C33), bronchus or lung (C34), ovarian cancer by the diagnosis of malignant neoplasm of ovary (C56).

Mortality was coded as a single binary variable (Y/N) combining the occurrence of deaths from any cause.

Statistical analyses

Missing data for variables at baseline were handled using multiple imputation by chained equations with missing at random assumption.⁴⁷ Through an iterative series of

predictive models built from observed variables, each binary and categorical variable was, respectively, imputed using logistic and polytomous regression models after 30 iterations to ensure completeness and robustness of the analyses.

The directed acyclic graph in [figure 1](#) describes the assumed relationships between lifetime unemployment exposure, the prevalence of cardiovascular risk factors at baseline, cardiovascular disease, cancer and mortality rates during follow-up and potential confounders that included sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions at baseline. The hypothesis was that part of the associations of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates was mediated by risk factors that were themselves associated with unemployment exposure. Note that cardiovascular, cancer and mortality rates referred to individual, not aggregate, data on the numbers of outcomes occurring during the follow-up.

The associations between lifetime unemployment exposure and the prevalence of risk factors at baseline were tested by logistic regression models with two levels of adjustment: models 1 were minimally adjusted for sex and age, and models 2 were additionally adjusted for social position and working conditions at baseline. The ORs calculated with these models were expressed over a one-unit change in unemployment exposure (ie, per unemployed quarter) and over the entire range of unemployed quarters. In this latter case, the OR represents the change in the odds of the outcome when the number of unemployed quarters varies from its minimum to its maximum value, that is, from 1 to 168. While the unit OR measures how much the odds of the outcome vary for each unemployed quarter, the range OR provides a broader picture of the influence of unemployment exposure by considering its entire range of variation.

In order to assess the possibility of reverse causation, where the occurrence of risk factors would have preceded unemployment exposure during lifetime, the mean, youngest and oldest ages at which participants were unemployed were compared with the ages at which risk factors were first reported (online supplemental figure 4). The youngest and oldest ages at which participants were unemployed were on average 28.7±9.1 (SD) and 40.6±12.0 years with a mean age of 35.0±9.5 years. In comparison, the ages at which the first reports of risk factors were made were on average 48.0±11.2 for hypertension, 48.4±10.9 for hypercholesterolaemia, 46.2±11.1 for hypertriglyceridaemia, 51.1±9.8 for diabetes and 36.8±12.3 years for depressive symptoms. Thus, unemployment episodes popped up on average much earlier than clinical risk factors during lifetime with a mean difference of approximately 10–15 years. Even the latest episodes occurred on average several years before the first reports of risk factors. The only exception was depressive symptoms that were first reported concomitantly with unemployment episodes. Unfortunately, no such chronology

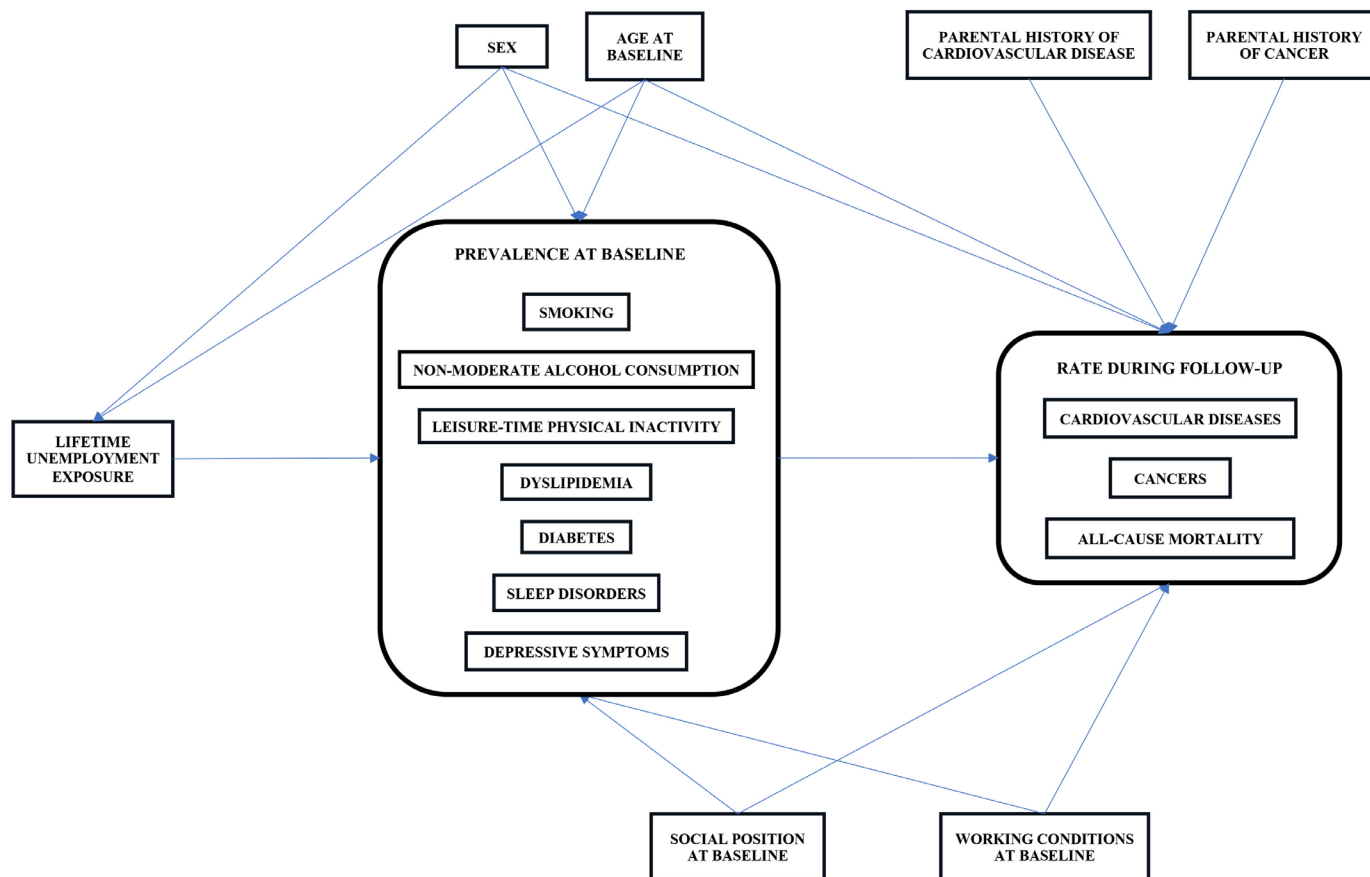


Figure 1 Directed acyclic graph showing the assumed relationships between lifetime unemployment exposure, the prevalence of risk factors at baseline, cardiovascular disease, cancer and all-cause mortality rates during follow-up and the potential confounders.

could be established between unemployment exposure and the first adoption of behavioural risk factors or the first occurrence of sleep disorders during lifetime due to the inherent imprecision of self-reporting of these risk factors.

The associations of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates were assessed by logistic regression models using two levels of adjustment: models 1 were minimally adjusted for sex, age and parental histories of cardiovascular disease and cancer, while models 2 were additionally adjusted for social position and working conditions at baseline. The ORs calculated with these models were also expressed per unemployed quarter and over the entire range of unemployed quarters as specified above.

The expected associations of risk factors at baseline with cardiovascular disease, cancer and mortality rates during follow-up were tested as confirmatory analyses. ORs expressed per unit change in risk factor levels and per change over the entire ranges of risk factor levels were calculated with logistic regression models adjusted for sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions at baseline.

Mediation analyses tested each risk factor separately and all together as long as they were associated at baseline

with lifetime unemployment exposure. Estimates for direct and indirect effects of unemployment exposure on cardiovascular, cancer and mortality rates were computed using logistic regression models adjusted for sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions at baseline. Note that these estimates were not standardised as standardisation of the coefficients prior to estimating the effects does not increase the performance of the estimates.⁴⁸ In addition to SE and 95% CIs that were obtained using bootstrapping with 5000 replicates, p values were calculated for the indirect effects using the Sobel test.⁴⁹ Statistical significance was fixed a priori at two-sided $p < 0.05$. Mediation analyses were performed with the PROCESS macro⁵⁰ combined with SPSS Statistics V.27 (IBM) that was used for the other analyses.

RESULTS

Characteristics of participants at baseline

Table 1 shows that the characteristics of participants and prevalence of risk factors at baseline were very similar in the whole set of participants who were exposed to unemployment during their lifetime ($n=99\,430$) and in the subset ($n=54\,679$) who were followed for 7 years after baseline to assess cardiovascular disease, cancer and

**Table 1** Characteristics of participants and prevalence of risk factors at baseline in the whole set of participants who were exposed to unemployment during their lifetime and in the subset who were followed for 7 years after baseline

		Participants exposed to unemployment		Participants exposed to unemployment and followed during 7 years	
		n=99 430		n=54 679	
		n	%	n	%
Sex	Women	53 883	54.2	29 636	54.2
	Men	45 547	45.8	25 043	45.8
Age (years)	18–39	32 464	32.7	17 169	31.4
	40–54	33 935	34.1	18 864	34.5
	55–75	33 031	33.2	18 646	34.1
Parental history of cardiovascular disease	No	75 169	75.6	41 119	75.2
	Yes	24 261	24.4	13 560	24.8
Parental history of cancer	No	66 220	66.6	36 690	67.1
	Yes	33 210	33.4	17 989	32.9
Social position	High	30 426	30.6	15 419	28.2
	Middle	42 059	42.3	23 293	42.6
	Low	26 945	27.1	15 967	29.2
Working conditions	Good	33 374	33.6	17 607	32.2
	Average	41 975	42.2	23 184	42.4
	Bad	24 081	24.2	13 888	25.4
Smoking	No	74 672	75.1	41 775	76.4
	Yes	24 758	24.9	12 904	23.6
Non-moderate alcohol consumption	No	88 194	88.7	48 118	88.0
	Yes	11 236	11.3	6561	12.0
Leisure-time physical inactivity	No	88 692	89.2	48 610	88.9
	Yes	10 738	10.8	6069	11.1
Obesity	No	85 410	85.9	47 024	86.0
	Yes	14 020	14.1	7655	14.0
Hypertension	No	58 962	59.3	31 768	58.1
	Yes	40 468	40.7	22 911	41.9
Dyslipidaemia	No	69 999	70.4	37 346	68.3
	Yes	29 431	29.6	17 333	31.7
Diabetes	No	93 464	94.0	51 125	93.5
	Yes	5966	6.0	3554	6.5
Sleep disorders	No	34 801	35.0	19 520	35.7
	Yes	64 629	65.0	35 159	64.3
Depressive symptoms	No	80 936	81.4	44 290	81.0
	Yes	18 494	18.6	10 389	19.0

mortality rates. The distribution of unemployed quarters (online supplemental figure 2) was also very similar with a mean (SD) of 13.22 (14.65) vs 13.73 (15.13).

Associations between lifetime unemployment exposure and the prevalence of risk factors at baseline

As reported in table 2, the prevalence of all risk factors at baseline was associated with lifetime unemployment exposure after adjustment for sex and age. However, additional adjustment for social position and working conditions at baseline

substantially decreased ORs to the point where obesity and hypertension were no longer associated with lifetime unemployment exposure. For the other risk factors, ORs (95% CIs) per change over the entire range of unemployed quarters varied from 1.39 (1.18 to 1.63) for sleep disorders to 10.8 (9.2 to 12.9) for smoking, which was the strongest factor associated with lifetime unemployment exposure together with non-moderate alcohol consumption (4.61 (3.67 to 5.78)) and depressive symptoms (5.67 (4.63 to 6.94)).

Table 2 ORs (95% CI) for the prevalence of risk factors at baseline according to lifetime unemployment exposure

	Unemployment	Models 1	P value	Models 2	P value
Smoking	Unit	1.0178 (1.0168 to 1.0188)	<0.0001	1.0143 (1.0133 to 1.0154)	<0.0001
	Range	19.222 (16.292 to 22.679)		10.854 (9.1580 to 12.863)	
Non-moderate alcohol consumption	Unit	1.0103 (1.0089 to 1.0116)	<0.0001	1.0091 (1.0078 to 1.0105)	<0.0001
	Range	5.5467 (4.4447 to 6.9081)		4.6100 (3.6684 to 5.7807)	
Leisure-time physical inactivity	Unit	1.0055 (1.0041 to 1.0069)	<0.0001	1.0032 (1.0018 to 1.0046)	<0.0001
	Range	2.5141 (1.9933 to 3.1617)		1.7209 (1.3505 to 2.1862)	
Obesity	Unit	1.0056 (1.0045 to 1.0067)	<0.0001	1.0006 (0.9994 to 1.0018)	0.31
	Range	2.5606 (2.1176 to 3.0917)		1.1104 (0.9077 to 1.3559)	
Hypertension	Unit	1.0031 (1.0021 to 1.0040)	<0.0001	0.9996 (0.9987 to 1.0006)	0.51
	Range	1.6812 (1.4393 to 1.9643)		0.9481 (0.8084 to 1.1120)	
Dyslipidaemia	Unit	1.0054 (1.0044 to 1.0064)	<0.0001	1.0020 (1.0010 to 1.0030)	<0.0001
	Range	2.4808 (2.1124 to 2.9138)		1.4068 (1.1927 to 1.6592)	
Diabetes	Unit	1.0084 (1.0069 to 1.0099)	<0.0001	1.0041 (1.0025 to 1.0056)	<0.0001
	Range	4.0702 (3.1862 to 5.1830)		1.9843 (1.5304 to 2.5634)	
Sleep disorders	Unit	1.0036 (1.0027 to 1.0046)	<0.0001	1.0019 (1.0010 to 1.0029)	<0.0001
	Range	1.8499 (1.5796 to 2.1681)		1.3897 (1.1824 to 1.6345)	
Depressive symptoms	Unit	1.0165 (1.0154 to 1.0177)	<0.0001	1.0104 (1.0092 to 1.0116)	<0.0001
	Range	15.575 (12.839 to 18.887)		5.6708 (4.6292 to 6.9405)	

ORs are expressed per unit change in unemployment exposure (ie, per unemployed quarter) or per change over the entire range of unemployed quarters. Models 1 were adjusted for sex and age. Models 2 were adjusted for sex, age, social position and working conditions at baseline.

Associations of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates during follow-up

Cardiovascular disease (n=668), cancer (n=1273) and mortality (n=399) rates during follow-up were, respectively, 1.22, 2.33 and 0.73%. [Table 3](#) shows that all these rates were associated with lifetime unemployment exposure after adjustment for sex, age and parental histories of cardiovascular disease and cancer. After further adjustment for social position and working conditions at baseline, ORs (95% CIs) per change over the entire range of unemployed quarters varied were 3.95 (2.06 to 7.33) for cardiovascular diseases, 2.54 (1.51 to 4.19) for cancers and 5.35 (2.42 to 11.3) for mortality.

Associations of risk factors at baseline with cardiovascular disease, cancer and mortality rates during follow-up

The expected associations of risk factors at baseline with cardiovascular disease, cancer and mortality rates during follow-up were confirmed after adjustment for sex, age and parental histories of cardiovascular disease and cancer, social position and working conditions at baseline ([table 4](#)). Smoking and alcohol consumption were strongly associated with cardiovascular disease, cancer and mortality rates, with ORs (95% CIs) per change over the entire range of unemployed quarters varying from 3.94 (2.30 to 6.65) to 7.16 (3.72 to 13.5). Blood cholesterol and triglycerides were strongly associated with cardiovascular disease rate with ORs of 6.84 (95% CI

Table 3 ORs (95% CIs) for cardiovascular disease, cancer and all-cause mortality rates during follow-up according to lifetime unemployment exposure

	Unemployment	Models 1	P value	Models 2	P value
Cardiovascular diseases	Unit	1.0100 (1.0063 to 1.0136)	<0.0001	1.0082 (1.0043 to 1.01219)	<0.0001
	Range	5.3915 (2.8987 to 9.7060)		3.9493 (2.0570 to 7.3290)	
Cancers	Unit	1.0070 (1.0040 to 1.0099)	<0.0001	1.0055 (1.0024 to 1.0085)	0.0006
	Range	3.2698 (1.9841 to 5.2838)		2.5404 (1.5088 to 4.1918)	
All-cause mortality	Unit	1.0141 (1.0097 to 1.0183)	<0.0001	1.0100 (1.0052 to 1.0145)	<0.0001
	Range	10.679 (5.1439 to 21.160)		5.3498 (2.4166 to 11.279)	

ORs are expressed per unit change in unemployment exposure (ie, per unemployed quarter) or per change over the entire range of unemployed quarters. Models 1 were adjusted for sex, age and parental histories of cardiovascular disease and cancer. Models 2 were adjusted for sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions at baseline.

**Table 4** ORs (95% CIs) for cardiovascular disease, cancer and all-cause mortality rates during follow-up according to risk factor levels at baseline

	Risk factor	Cardiovascular diseases	P value	Cancers	P value	All-cause mortality	P value
Smoking (items/day)	Unit	1.0198 (1.0132 to 1.0263)	<0.0001	1.0138 (1.0083 to 1.0191)	<0.0001	1.0186 (1.0101 to 1.0268)	<0.0001
	Range	7.1633 (3.7197 to 13.469)		3.9403 (2.2986 to 6.6506)		6.3638 (2.7458 to 14.139)	
Alcohol consumption (drinks/day)	Unit	1.0741 (1.0340 to 1.1123)	0.0004	1.0742 (1.0410 to 1.1062)	<0.0001	1.0870 (1.0376 to 1.1330)	0.0007
	Range	5.1834 (2.1583 to 11.575)		5.1909 (2.5205 to 10.194)		6.8159 (2.3380 to 17.700)	
Leisure-time physical inactivity score	Unit	1.1080 (1.0541 to 1.1646)	<0.0001	1.0703 (1.0318 to 1.1102)	0.0003	1.1759 (1.1026 to 1.2542)	<0.0001
	Range	1.8511 (1.3724 to 2.4956)		1.5040 (1.2072 to 1.8730)		2.6447 (1.7971 to 3.8925)	
Blood cholesterol (mmol/l)	Unit	1.1789 (1.0979 to 1.2651)	<0.0001	0.9994 (0.9469 to 1.0546)	0.98	1.0953 (0.9971 to 1.2043)	0.06
	Range	6.8419 (2.9777 to 15.594)		0.9941 (0.5288 to 1.8613)		2.8978 (0.9674 to 8.7736)	
Blood triglycerides (mmol/l)	Unit	1.3285 (1.2243 to 1.4353)	<0.0001	1.0455 (0.9638 to 1.1301)	0.28	1.1275 (0.9961 to 1.2644)	0.06
	Range	9.2207 (4.8685 to 16.882)		1.4167 (0.7500 to 2.6024)		2.5561 (0.9705 to 6.2626)	
Blood glucose (mmol/l)	Unit	1.0996 (1.0176 to 1.1823)	0.02	1.0750 (1.0095 to 1.1411)	0.03	1.2226 (1.1236 to 1.3218)	<0.0001
	Range	2.5834 (1.1908 to 5.3286)		2.0601 (1.0996 to 3.7409)		7.4490 (3.2042 to 16.236)	
Sleep duration (hours/day)	Unit	1.0370 (1.0002 to 1.0753)	0.04	1.0584 (1.0313 to 1.0863)	<0.0001	1.0442 (0.9981 to 1.0924)	0.06
	Range	1.4927 (1.0024 to 2.2237)		1.8688 (1.4047 to 2.4869)		1.6092 (0.9795 to 2.6450)	
Depression score	Unit	1.0143 (1.0048 to 1.0235)	0.003	1.0031 (0.9961 to 1.0100)	0.38	1.0216 (1.0099 to 1.0329)	0.0003
	Range	2.3465 (1.3366 to 4.0411)		1.2065 (0.7919 to 1.8187)		3.6064 (1.8133 to 6.9766)	

ORs are expressed per unit change in risk factor levels or per change over the entire ranges of risk factor levels. Models were adjusted for sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions at baseline.

2.98 to 15.6) and 9.22 (95% CI 4.87 to 16.9), respectively. Blood glucose was strongly associated with mortality rate with an OR of 7.45 (95% CI 3.20 to 16.2). Several other significant associations were observed with ORs of smaller magnitude (table 4).

Mediating roles of risk factors at baseline in the associations of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates during follow-up

When testing separately the mediating role of each risk factor, smoking was the strongest mediator of the associations of lifetime unemployment exposure with cardiovascular disease and cancer rates, explaining 10.8 and 10.6% of the associations, respectively (table 5). Smoking also explained 8.7% of the association with mortality rate. Other significant mediators were alcohol consumption that explained 5.0%, 5.6% and 3.4% of the associations with cardiovascular disease, cancer and mortality rates, respectively; depressive symptoms that explained 7.7% and 10.2% of cardiovascular disease and mortality rates, respectively; leisure-time physical inactivity that explained 3.5%, 3.4% and 3.7% of the associations with cardiovascular disease, cancer and mortality rates, respectively; and blood triglycerides that explained 5.9% of the association with cardiovascular disease rate. The percentages of the associations mediated by risk factors when these latter were tested all together were 21.1% (estimates (95% CIs) of the direct and indirect effects were 0.0075 (0.0022 to 0.0128), $p=0.005$ and 0.0020 (0.0011 to 0.0027), $p<0.0001$) for cardiovascular disease rate, 22.4% (0.0052 (0.0011 to

0.0093), $p=0.01$ and 0.015 (0.0009 to 0.0020), $p<0.0001$) for cancer rate, 17.7% (0.0102 (0.0035 to 0.0169), $p=0.003$ and 0.0022 (0.0011 to 0.0031), $p<0.0001$) for mortality rate.

DISCUSSION

In agreement with previous reports,^{10–13 15–17} the present analyses confirm that high unemployment exposure during lifetime is associated with an increased prevalence of several common risk factors after adjustment for major confounders. Although observational, these results support the possibility of a causal relationship given that unemployment exposure largely preceded or was concomitant in average with the first occurrence of clinical risk factors during lifetime. Although it was not possible to establish such chronology between unemployment exposure and the first adoption of risky behaviours during lifetime, several studies suggest that unemployment exposure increases the incidence of smoking and high alcohol consumption.^{51–54}

The present analyses also confirm that high unemployment exposure during lifetime is associated with increased cardiovascular disease, cancer and mortality rates after adjustment for major confounders.^{1–5 7–9 18} The main finding is that several risk factors that are associated with unemployment mediate in part the associations of lifetime unemployment exposure with cardiovascular disease, cancer and mortality rates. Smoking seems to

Table 5 Mediating role of each risk factor at baseline in the associations of lifetime unemployment exposure with cardiovascular disease, cancer and all-cause mortality rates during follow-up

		Effect	Estimate	SE	95% CI	P value	% mediation
Smoking (items/day)	Cardiovascular diseases	Direct	0.0083	0.0020	0.0044 to 0.0122	<0.0001	89.2
		Indirect	0.0010	0.0002	0.0007 to 0.0014	<0.0001	10.8
	Cancers	Direct	0.0059	0.0016	0.0028 to 0.0089	0.0002	89.4
		Indirect	0.0007	0.0001	0.0004 to 0.0010	<0.0001	10.6
	All-cause mortality	Direct	0.0105	0.0024	0.0058 to 0.0151	<0.0001	91.3
		Indirect	0.0010	0.0002	0.0005 to 0.0014	<0.0001	8.7
Alcohol consumption (drinks/day)	Cardiovascular diseases	Direct	0.0076	0.0022	0.0034 to 0.0118	0.0004	95.0
		Indirect	0.0004	0.0001	0.0002 to 0.0005	0.0006	5.0
	Cancers	Direct	0.0067	0.0016	0.0035 to 0.0100	<0.0001	94.4
		Indirect	0.0004	0.0001	0.0002 to 0.0005	<0.0001	5.6
	All-cause mortality	Direct	0.0114	0.0026	0.0064 to 0.0164	<0.0001	96.6
		Indirect	0.0004	0.0001	0.0001 to 0.0006	0.0009	3.4
Leisure-time physical inactivity score	Cardiovascular diseases	Direct	0.0083	0.0020	0.0044 to 0.0122	<0.0001	96.5
		Indirect	0.0003	0.0001	0.0001 to 0.0005	0.0006	3.5
	Cancers	Direct	0.0057	0.0016	0.0026 to 0.0088	0.0004	96.6
		Indirect	0.0002	0.0001	0.0001 to 0.0003	0.002	3.4
	All-cause mortality	Direct	0.0105	0.0024	0.0058 to 0.0152	<0.0001	96.3
		Indirect	0.0004	0.0001	0.0002 to 0.0007	<0.0001	3.7
Blood cholesterol (mmol/l)	Cardiovascular diseases	Direct	0.0086	0.0019	0.0048 to 0.0124	<0.0001	98.9
		Indirect	0.0001	0.0001	0.0001 to 0.0003	0.001	1.1
	Cancers	Direct	0.0057	0.0016	0.0026 to 0.0087	0.0003	99.9
		Indirect	0.0000	0.0000	0.0000 to 0.0001	0.93	0.1
	All-cause mortality	Direct	0.0105	0.0023	0.0060 to 0.0151	<0.0001	99.1
		Indirect	0.0001	0.0001	0.0000 to 0.0002	0.11	0.9
Blood triglycerides (mmol/l)	Cardiovascular diseases	Direct	0.0080	0.0020	0.0042 to 0.0119	<0.0001	94.1
		Indirect	0.0005	0.0001	0.0004 to 0.0007	<0.0001	5.9
	Cancers	Direct	0.0057	0.0016	0.0026 to 0.0087	0.0003	98.3
		Indirect	0.0001	0.0001	-0.0001 to 0.0002	0.32	1.7
	All-cause mortality	Direct	0.0103	0.0024	0.0057 to 0.0149	<0.0001	98.1
		Indirect	0.0002	0.0001	0.0000 to 0.0004	0.06	1.9
Blood glucose (mmol/l)	Cardiovascular diseases	Direct	0.0086	0.0019	0.0048 to 0.0124	<0.0001	99.9
		Indirect	0.0000	0.0000	0.0000 to 0.0001	0.39	0.1
	Cancers	Direct	0.0056	0.0016	0.0025 to 0.0087	0.0003	99.9
		Indirect	0.0000	0.0000	-0.0000 to 0.0001	0.39	0.1
	All-cause mortality	Direct	0.0106	0.0024	0.0059 to 0.0152	<0.0001	99.9
		Indirect	0.0000	0.0000	-0.0000 to 0.0001	0.34	0.1
Sleep duration (hours/day)	Cardiovascular diseases	Direct	0.0090	0.0020	0.0051 to 0.0129	<0.0001	99.9
		Indirect	0.0000	0.0000	-0.0001 to 0.0000	0.31	0.1
	Cancers	Direct	0.0055	0.0016	0.0024 to 0.0087	0.0006	99.9
		Indirect	0.0000	0.0000	-0.0001 to 0.0000	0.19	0.1
	All-cause mortality	Direct	0.0109	0.0024	0.0062 to 0.0156	<0.0001	99.9
		Indirect	0.0000	0.0000	-0.0001 to 0.0000	0.31	0.1

Continued



Table 5 Continued

		Effect	Estimate	SE	95% CI	P value	% mediation
Depression score	Cardiovascular diseases	Direct	0.0084	0.0023	0.0040 to 0.0128	0.0002	92.3
		Indirect	0.0007	0.0002	0.0002 to 0.0011	0.005	7.7
	Cancers	Direct	0.0053	0.0018	0.0017 to 0.0089	0.004	98.1
		Indirect	0.0001	0.0002	-0.0002 to 0.0005	0.51	1.9
	All-cause mortality	Direct	0.0088	0.0029	0.0031 to 0.0144	0.002	89.8
		Indirect	0.0010	0.0003	0.0004 to 0.0015	0.0005	10.2

Models were adjusted for sex, age, parental histories of cardiovascular disease and cancer, social position and working conditions at baseline.

be especially involved, which is not surprising given that unemployment may influence smoking behaviour in many ways, increasing the risk of relapse after cessation, the odds of starting smoking, smoking intensity or decreasing the odds of cessation.^{12 51 53} Alcohol consumption also has a significant mediating effect on cardiovascular disease, cancer and mortality rates, which is in line with the promoting effect of unemployment on drinking behaviour.^{12 54 55} Depressive symptoms are worth mentioning considering their mediating effects on cardiovascular disease rate and even more on mortality rate, this latter effect being also probably related to an increased suicide rate.⁵⁶ However, the mediating effects of each risk factor remain modest, explaining at most 10% of the associations and reaching only 20% when considering risk factors all together. This suggests that unemployment may increase cardiovascular disease, cancer and mortality rates not only by overexposure to common risk factors but also through other pathways that have yet to be defined. Identifying these pathways may not be so easy as the potential stressful effects of unemployment are numerous and entangled. For example, neurohormonal changes such as elevated cortisol levels might be involved to some extent among many others.⁵⁷

The present study has both strengths and limitations. Among the strengths is that potential confounding effects of social position and working conditions have been taken into account, which is critical given their strong interrelationships with unemployment exposure¹⁸ and their powerful influence on the incidence of risk factors and deaths.^{25-31 34-36 38-41} Another strength is that, except for risky behaviours, diagnoses of risk factors, cardiovascular diseases, cancers and deaths were based on clinical data. This is an important issue as questions have been raised concerning the validity of self-reported data for exploring the relationships between unemployment and health.^{58 59} Among the limitations is the external validity of the findings, which is not guaranteed given that they were obtained in a cohort which was not representative of the French population. The main reason for this lack of representativeness was the inclusion rate, which was low, although in line with those observed in other large population-based cohorts when participants are required to visit a medical centre for health-related exams.⁶⁰ This

resulted in the preferential selection of socially privileged people despite the stratified sampling strategy that tried to compensate for the lower response rate of individuals with low socioeconomic status.⁴² This selection bias, which increased the proportion of socially privileged individuals, likely weakens the relationships between unemployment exposure, disease risk and mortality. Indeed, although several major confounders which characterise socially privileged individuals (high education, high-skilled occupation, high income, good working conditions, low exposure to risky behaviours) have been adjusted for, these individuals often have a high health-related knowledge, a strong importance given to the care of one's own health, a high capacity to optimise health service use, a high sense of control over life and problem-solving and a high resilience to the negative effects of psychosocial problems.⁶¹ Therefore, they are better off to cope with the various consequences of unemployment and as a result would be less prone to subsequent health issues. The second limitation is whether the estimates of the relationships reported in the present study are relevant to other high-income countries. Indeed, the relationships between unemployment exposure, health and mortality are strongly influenced by the social security and health-care systems⁶² which vary substantially from one country to another. Although France provides an average unemployment compensation in terms of the replacement rate of wage, the duration of unemployment insurance benefit or the waiting period before getting the benefit after job loss,⁶³ its healthcare system is above average⁶⁴ and it is difficult to know to which extent the estimates can be extrapolated to other countries. The third limitation is that even though the lifetime chronology favours the hypothesis that unemployment exposure rises cardiovascular disease, cancer and mortality rates in part by increasing the prevalence of common risk factors, the observational nature of the analyses precludes the inference of causal relationships. Indeed, despite the adjustments for major potential confounders, unmeasured or uncontrolled factors may still significantly influence the observed associations and their interpretation. The fourth limitation is that the present analyses did not assess the linearity of the relationships between unemployment exposure, disease risk and mortality. Indeed, it has been

suggested using aggregate data that these relationships might be U-shaped due to differential responsiveness of individuals according to the level of unemployment.⁶⁵ The fifth limitation is that the present study analysed the cumulative effect of unemployed quarters over a lifetime but did not assess the possibility that unemployment may have a differential effect on the outcomes according to the age of exposure. The sixth limitation is that, despite the large population size, the lack of statistical power precluded the assessment of specific types of cardiovascular diseases and cancers, as well as the causes of death, associated with unemployment exposure.

In conclusion, even though the relatively short follow-up may not fully capture the long-term health implications of lifetime unemployment exposure, the analyses show that the associations of unemployment exposure with cardiovascular disease, cancer and mortality rates are mediated in part by an increased prevalence of common risk factors such as smoking, alcohol consumption and depression. However, these mediating effects are modest, pointing to other unidentified major pathways linking unemployment to health.

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Ethics approval This study involves human participants and all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975 as revised in 2008. All procedures have been approved by the Institutional Review Board of the French National Institute of Health (Opinion no 01-011, then no 21-842) and authorised by the French Data Protection Authority (Authorisation #910486). Participants gave informed consent to participate in the study before taking part.

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