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ORIGINAL RESEARCH

Association between occupational solvent exposure and cognitive performance in the French CONSTANCES study

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2019-106132).

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Received 7 August 2019
Revised 22 January 2020
Accepted 27 January 2020
Published Online First 19 February 2020

Check for updates

To cite: Letellier N, Choron G, Artaud F, *et al*. *Occup Environ Med* 2020;**77**:223–230.

ABSTRACT

Objective The objective of this study was to evaluate the association between occupational exposure to solvents and cognitive performance in middle-aged and early-ageing participants, taking into account the working environment.

Methods In the French Cohorte des consultants des Centres d'examens de santé (CONSTANCES) cohort, 41 854 participants aged 45–**69** years completed a self-reported, lifetime occupational exposure questionnaire. Exposure to solvents (gasoline for hand washing, trichloroethylene, white spirit, cellulosic thinner) was first considered as a binary variable (exposed/not exposed). We computed number of solvent types to which participants were exposed, solvent exposure time and delay since last exposure. Cognitive performance was assessed and analysed in reference to norms of neuropsychological battery previously established in CONSTANCES according to age, sex and education. Multiple linear and modified Poisson regression were used to estimate the associations between solvent exposure and cognitive performance adjusting for individual and environmental characteristics, and working conditions (night shift, repetitive and noisy work).

Results Men had a greater risk of global cognitive impairment when they were exposed to gasoline (relative risk (RR)=1.12, 95% CI 1.03 to 1.22), white spirit (RR=1.14, 95% CI 1.05 to 1.25) or cellulosic thinner (RR=1.17, 95% CI 1.06 to 1.31) at the workplace, even after adjusting for confounders. Women exposed to white spirit or exposed for more than 20 years had poorer global cognitive performance.

Conclusion These findings strengthen our understanding of the detrimental effect of solvent exposure on cognitive health not only in men but also in women for the first time, in a large general population middle-aged and early-ageing sample from France, taking into account working conditions.

Key messages

What is already known about this subject?

- ► Since the 1980s, the neurotoxicity of organic solvents has been highlighted.
- ► However, in observational studies, gaps remain due to methodological heterogeneity and limitations of previous studies. Most studies were performed in occupational setting, included small numbers of participants, with limited adjustment for confounders or were restricted to men.

What are the new findings?

- ► Associations between occupational solvent exposures and cognitive performance in the CONSTANCES cohort are the first established in a large general population sample of middle-aged to early-aging volunteers (age range: 45 to 69 years).
- ► Occupational solvent exposure is associated with cognitive impairment, independently of individual characteristics and working conditions.
- ► Given the large number of women in this study, it is to our knowledge the first to explore the detrimental effects of solvents on cognition.

How might this impact on policy or clinical practice in the foreseeable future?

- ► These findings strengthen the evidence in favour of detrimental effects of solvents on cognitive health in men and women, in relatively young population.

INTRODUCTION

The toxicity of organic solvents represents a public health problem despite regulations that tend to limit their use.[1] Solvents are used as degreasers, adjuvants, thinners, cleaners or purifiers, and represent common occupational exposures. Millions of workers are exposed to organic solvents in a wide range of processes; in industrialised countries, occupational exposure prevalence is around 8%.[2 3]

Since the 1980s, the neurotoxicity of organic solvents has been demonstrated.[4–7] Chronic exposure can induce symptoms of nervous system damage including headache, fatigue, memory and concentration impairment, irritability, depression and personality changes.[8] A meta-analysis of 46 cross-sectional studies showed that solvent exposure was associated with deficits in cognitive function, particularly for attention and procedural speed.[9] Results from neuroimaging studies support a central neurotoxicity.[10 11]

However, previous studies on the relation between solvent exposure and cognitive impairment provided inconsistent results,[12] exposure–effect relationships were characterised by inconsistent patterns[9] and gaps remain due to their methodological heterogeneity and limitations.[13] Most studies were performed in occupational settings,[4–6 14] included small numbers of participants,[14–16] with limited adjustment for confounders[9] or were restricted to men.[5 6]

The objective of this analysis of data from the Cohorte des consultants des Centres d'examens de santé (CONSTANCES) study was to examine the association between occupational exposure to solvents and cognitive performance in a large French cohort of middle-aged to early-ageing men and women from the general population, before the onset of clinical symptoms of neurodegenerative diseases and loss of autonomy, taking into account working conditions in addition to the socioeconomic environment and individual characteristics.

MATERIALS AND METHODS

Participants

This cross-sectional study used baseline data from the CONSTANCES cohort, a large population-based prospective cohort of French adults aged 18–69 years at recruitment, initiated in 2012 in 23 Health Screening Centres (HSC) in the principal regions of France. Details on cohort recruitment and data collection are available elsewhere.[17] Participants were randomly selected among members of the CNAM health insurance ('Caisse Nationale d'Assurance Maladie') that is salaried workers, unemployed or retired and their family (over 85% of the French population), thus excluding agricultural and self-employed workers. More than 200 000 subjects have been included over a 7-year period, between 2012 and February 2019. At inclusion, participants have completed questionnaires including social and demographic characteristics and have benefited for a health examination in HSC.

In the present study, we restricted the analysis to participants aged 45 years and older, who benefited from a standardised cognitive and physical assessment by trained neuropsychologists[18]; analyses are based on data available for data analysis in January 2019.

Occupational solvent exposure

At baseline, participants self-reported lifetime occupational solvent exposure. They were asked whether they had ever used any solvents, thinners, degreasers or disinfectants (to clean equipment or hand washing) for four main types of organic solvents available (gasoline for hand washing, trichlorethylene, white spirit, cellulosic thinner); if yes, they provided information about the start and end year of exposure. This allowed us to compute the number of types of solvents to which participants were exposed (0 to 4; as few women were exposed to 2, 3 or 4 types of solvents, thus they were grouped together). We also computed the cumulative exposure time to any type of solvent and categorised it in three classes (<10/10 to <20/≥20 years) as well as the delay since last exposure (time between the date of cognitive testing and the last exposure in two groups: ≥5 years/currently or <5 years).

Cognitive function

At inclusion, cognitive function was assessed by trained neuropsychologists using a standardised battery of cognitive tests evaluating global cognitive function, episodic verbal memory, language abilities and executive functions.[19]

The French version of the Mini Mental State Examination (MMSE)[20] was used to assess global cognitive function. To assess episodic verbal memory, we used the Free and Cued Selective Reminding Test (FCRST)[21]; for this study, we considered the delayed free recall score (number of freely retrieved words during the delayed phase). To evaluate language abilities, the Verbal Fluency Tasks (VFT)[22] was used by counting the number of words named in 1 min (semantic and phonemic fluency tasks). The two parts of the Trail Making Test (TMT-A and TMT-B, coded as time in seconds) assessed executive function and shifting abilities.[23] The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale–Revised[24] that explores attention, processing speed and executive function. For each tests, the cut-off of the normative neuropsychological tests previously established in CONSTANCES according to sex, age and level of education[19] allowed us to defined poor performance (based on a score below or equal to the 25th percentile of this distribution, greater than or equal to the 75th percentile for TMT).

We constructed a global cognitive score using principal component analysis (PCA). It was defined as the first axis of a PCA of the six scores previously described: FCRST, VFT (semantic and phonemic), TMT-A and TMT-B, and DSST. The first axis explained 47% of the variance for men and 44% for women, and it was characterised by positive scores and high weights for FCRST, VFT (semantic and phonemic) and DSST, and by negative scores for TMT-A and TMT-B. The position of the participants on this axis defines their degree of global cognitive performance: lower score corresponds to worse cognitive performance.

Lifetime working conditions

Regarding working environment, we used the following variables to characterise lifetime professional constraints: night-shift work (shift work with alternating hours or working hours/travel time often requiring not to sleep during the night at least 50 days/year); repetitive work (under time constraints); noisy work (working in an atmosphere that sometimes requires raising one's voice to speak to a neighbour/interlocutor within 2/3 metres, or working with/near noisy tools, machines or vehicles).

Covariates

Individual covariates included sociodemographic factors: age (in years), education (no diploma or certificate of primary, secondary education, high school graduation, up to 2 years of university education, master degree or more), marital status and income. Lifestyle factors included smoking (never, past, current), alcohol consumption (Alcohol Use DIsorders Test (AUDIT) questionnaire[18]: abstinent, neither abuse or dependence, abuse, dependence), and body mass index (BMI, kg/m^2; underweight: BMI<18.5, normal: 18.5≤BMI<25, overweight: 25≤BMI<30, obesity: BMI≥30). Comorbidities included high blood pressure (HBP; blood pressure higher than 140/90 mm Hg or history of hypertension), history of diabetes, of cardiovascular disease (CVD: stroke, angina pectoris, myocardial infarction, arteritis of the lower limbs, others), of respiratory disease (chronic bronchitis, emphysema, asthma, other) and depressive symptomatology assessed by a score greater than or equal to 16 on the Center for Epidemiological Studies–Depression (CESD) scale.[25]

In addition to these individual covariates, in order to characterise neighbourhood socioeconomic status, we also included a composite deprivation index (French deprivation index (FDep09)) based on four variables (median household income, percentage of high school graduates, percentage of blue-collar workers and unemployment rate).[26]

Statistical analyses

All analyses were stratified by sex because of large differences in exposure prevalence between men and women.

We first performed a multiple linear regression to model global cognitive score that was normally distributed. Afterwards, for all cognitive tests dichotomised at the 25th percentile (75th percentile for TMT), we used modified Poisson regression with a robust error variance to estimate relative risk (RR) and their 95% CI.[27] Separate models were considered for each combination of types of solvents and cognitive test. Covariates included in the multivariate analysis were selected based on univariate analyses (p<0.20) and the literature.[28] For both multiple linear and modified Poisson regression, model 1 (M1) included sociodemographic/lifestyle characteristics and comorbidities associated with solvent exposure (age, level of education, marital status, income, smoking, alcohol consumption, BMI, HBP, cardiovascular disease, respiratory diseases, CESD) and the deprivation index (FDep09). Model 2 (M2) additionally included other occupational exposure (night shift, repetitive and noisy work) that are associated with cognitive function.

The possible influence of exclusion of volunteers with missing data for covariates and occupational exposure was evaluated in sensitivity analyses by using multiple imputation. Missing values for covariates and solvent exposures were imputed by multiple imputation (with the Markov chain Monte Carlo method; M=5 imputations).

All analyses were performed using SAS V.9.4.

RESULTS

Study population

Among the 74 692 volunteers aged 45 and older, we excluded those who do not speak French and subjects whose cognitive performance was first recorded on paper forms with manual timing of the test (n=3322). Analyses were restricted to subjects with complete and reliable cognitive tests (n=58 288). We also excluded outlier data for cognitive tests (MMSE below 10, TMT below 10 s (A and B) or higher than 130 (A) or 300 s (B)) and missing data for exposure variables and covariables. Finally, the analytical sample included 41 854 subjects with complete data (online supplementary figure 1).

Demographic differences between the main cohort and the final study population have been presented in online supplementary table 1. Compared with the excluded people, included participants were more often men, younger, more educated, wealthier, more often white-collar job and healthier (p<0.0001).

Characteristics of 41 854 individuals included in the study sample are shown in table 1; 51.7% were women, and the median age (IQR) for women was 57 (51–63) years and 57.5 (51.5–63.5) years for men. Nearly 50% of men and women had high school graduation, and 3.1% of women and 12.7% of men were blue-collar workers. About 34% of women and 38% of men were retired or withdrawn from business. Overweight and history of CVD, respiratory disease and HBP were more frequent in men than women; conversely, depressive symptoms were more frequent in women than men. Night-shift and noisy work were more frequent in men than in women, while repetitive work was equally frequent in both sex.

Occupational solvent exposure

The most exposed occupation class is the working class, 34% of blue-collar workers were exposed to at least one solvent (n=1058), in comparison with 12% of artisans, and 5% of executives and employees. Overall, 16.8% of men (n=3392) were

Table 1 Individual characteristics by sex (n=41 854)

Individual characteristics, n (%)	Men (n=20 234)	Women (n=21 620)
Sociodemographic and socioeconomic factors		
Age (years)*	57.5 (51.5–63.5)	57.0 (51–63)
Education level		
No diploma or certificate of primary education	1787 (8.8)	2137 (9.9)
Secondary education	5076 (25.1)	3855 (17.8)
High school graduation	3086 (15.3)	3986 (18.4)
Up to 2 years of university education	5681 (28.1)	8281 (38.3)
Master degree or more	4604 (22.8)	3361 (15.6)
Civil status		
Single	2329 (11.5)	2842 (13.2)
Married	15 051 (74.4)	14 128 (65.4)
Divorced or separated	2539 (12.6)	3660 (16.9)
Widowed	315 (1.6)	990 (4.6)
Income <€2100	2459 (12.2)	3822 (17.7)
Retired	7592 (37.5)	7293 (33.7)
Occupation (PCS) (n=29 447)		
Farmer or craftsman	560 (2.8)	338 (1.6)
Executive, intellectual profession	8129 (41.2)	4968 (23.7)
Middle-level profession	5763 (29.2)	7382 (35.2)
Employee	1902 (9.7)	6694 (31.9)
Blue-collar worker	2499 (12.7)	644 (3.1)
Never worked or other	636 (3.1)	727 (3.4)
Lifestyle and health factors		
Alcohol		
Abstinent	248 (1.2)	752 (3.5)
No abuse or dependence	15 517 (76.7)	18 229 (84.3)
Abuse	3475 (17.2)	2223 (10.3)
Dependence	994 (4.9)	416 (1.9)
Smoking status		
Never	7783 (38.5)	10 909 (50.5)
Current	2587 (12.8)	2827 (13.1)
Past	9864 (48.8)	7884 (36.5)
BMI (kg/m^2)		
Underweight (<18.5)	1132 (5.6)	1673 (7.7)
Normal (18.5–<25)	7441 (36.8)	11 876 (54.9)
Overweight (≥25–30)	8856 (43.8)	5499 (25.4)
Obese (>30)	2805 (13.9)	2572 (11.9)
Hypertension	9559 (47.2)	6651 (30.8)
Diabetes	832 (4.1)	368 (1.7)
History of vascular disease	2251 (11.1)	1588 (7.4)
History of respiratory disease	2744 (13.6)	2668 (12.3)
Depressive syndrome	2661 (13.2)	5127 (23.7)
Working conditions		
Night-shift work	4659 (23.0)	3259 (15.1)
Repetitive work	1393 (6.9)	1390 (6.4)
Noisy work	7263 (35.9)	4342 (20.8)
Cognitive performances*		
MMSE (0–30)†	29 (28–29)	29 (28–30)
FCRST (0–48)†	32 (28–35)	34 (31–38)
Semantic VFT (words in 1 min)†	23 (20–28)	24 (20–28)
Phonemic VFT (words in 1 min)†	15 (12–18)	16 (13–19)
TMT-A (max 180 s)†	31 (25–39)	31 (25–38)
TMT-B (max 180 s)†	60 (48–77)	58 (47–72)
DSST score (0–135)†	64 (56–74)	70 (61–79)

*Median (IQR).
†Theoretical range.
BMI, body mass index; DSST, Digit Symbol Substitution Test; FCRST, Free and Cued Selective Reminding Test; MMSE, Mini Mental State Examination; PCS, French nomenclature of occupations and socio-professional categories; TMT, Trail Making Test; VFT, Verbal Fluency Tasks.

Table 2 Occupational solvent exposure by sex (n=41 854)

Occupational solvent exposure, n (%)	Men (n=20 234)	Women (n=21 620)
Type of solvents		
Gasoline for hand washing	1567 (7.7)	163 (0.8)
Trichloroethylene	2184 (10.8)	293 (1.4)
White spirit	1614 (8.0)	224 (1.0)
Cellulosic thinner	886 (4.4)	92 (0.4)
No. of type of solvents*	(n=19 546)	(n=21 325)
Exposed to one type only	1510 (7.7)	335 (1.6)
Exposed to two different types	729 (3.7)	91 (0.4)
Exposed to three different types	454 (2.3)	34 (0.2)
Exposed to four different types	304 (1.6)	12 (0.1)
Cumulative exposure time	(n=19 566)	(n=21 291)
1–10 years	1118 (5.7)	205 (1.0)
10–20 years	750 (3.8)	111 (0.5)
>20 years	1158 (5.9)	124 (0.6)
Delay since last exposure	(n=19 545)	(n=21 324)
>5 years	2188 (11.2)	275 (1.3)
<5 years or current	808 (4.1)	196 (0.9)

*The variable number of types of solvents was grouped into three classes for women (not exposed, one and two or more).

occupationally exposed to at least one of the four solvents examined: 7.7% were exposed to gasoline, 10.8% to trichloroethylene, 8.0% to white spirit, 4.4% to cellulosic thinner (table 2). Among women, 2.5% (n=550) were exposed to at least one of the four solvents: 0.8% to gasoline, 1.4% to trichloroethylene, 1.0% to white spirit, 0.4% to cellulosic thinner. In men, 1.6% were exposed to the four solvents, 2.3% to three, 3.7% to two and 7.7% to one only. In contrast, few women (0.7%) were exposed to more than one solvent. The average cumulative number of years of exposure was 17.3 years (SD 12.8) for men and 13.8 years (SD 11.1) for women. As expected, the main occupational groups exposed to solvents were maintenance of industrial equipment, building, mechanics, metalworking, manufacturing industry, technicians, electricity and furnishing (data not shown).

Cognitive performance and types of solvents

In multiple linear regression models adjusted for working environment, health and socioeconomic status (table 3), men had poorer global cognitive performance when they were exposed to gasoline, trichloroethylene, white spirit and cellulosic thinner. A similar pattern was observed for the DSST (data not shown). Figure 1 shows the association between solvent exposure and cognitive impairment (<25th percentile, >75th percentile for the TMT). In men, significant associations were observed for all solvents. Nevertheless, in comparison with the other solvents, the association with trichloroethylene is less clear in modified Poisson regression. Compared with unexposed men, those exposed to gasoline (RR=1.12, 95% CI 1.03 to 1.22), white spirit (RR=1.14, 95% CI 1.05 to 1.25) or cellulosic thinner (RR=1.17, 95% CI 1.06 to 1.31) were at greater risk of global cognitive impairment, independently of individual and environmental characteristics and working conditions.

Women had poorer cognitive performance (for the global cognitive score) when they were exposed to white spirit (table 3) and (for the DSST) when they were exposed to gasoline (RR=1.41, 95% CI 1.04 to 1.91) (online supplementary figure 2), independently of working conditions.

For both sex, the adjustment for working conditions (night-shift work, repetitive work, noisy work) reduced the strength of the associations for all cognitive domains.

Cognitive performance and number of types of solvents

In men, we observed significant exposure–effect relationships between the number of types of solvent and cognition (table 3 and figure 2). The more men were exposed to a large number of solvents, the worse their global cognitive performance (p trend=<0.0001). For instance, for the DSST, compared with unexposed men, the RR for men exposed to one type of solvent was 1.16 (95% CI 1.03 to 1.31), while it was 1.54 (95% CI 1.25 to 1.89) for four, even after adjustment for working conditions (figure 2).

In women, no exposure–effect relationships between number of solvents and cognitive performance were evident (online supplementary figure 3).

Cognitive performance and cumulative exposure time

In men, significant exposure–effect relationships between cumulative exposure time and cognitive performance were observed (table 3 and figure 2). The longer men were exposed to solvents, the worse their cognitive performances independently of individual characteristics, socioeconomic environment and working conditions (p<0.0001). Furthermore, men with the longest duration of exposure (>20 years) had a greater risk of cognitive impairment compared with those unexposed, even after additional adjustment for working environment (figure 2). For example, compared with unexposed individuals, men exposed to solvents for more than 20 years were at greater risk of having poorer MMSE performance (RR M2=1.20, 95% CI 1.04 to 1.38).

In table 3, women exposed for more than 20 years had poorer global cognitive performance (β=−0.38, 95% CI −0.63 to −0.13) in comparison with those unexposed and this association stayed significant even after adjustment for working conditions (β=−0.31, 95% CI −0.57 to −0.06). With Poisson regression, no associations were observed (online supplementary figure 3).

Cognitive performance and delay since last exposure

The global cognitive score was lower in men currently exposed and exposed more than 5 years ago, compared with those unexposed (table 3). Similar results were observed when considering the different cognitive domains in men (figure 2). For instance, for the DSST, men currently exposed (RR M2=1.33, 95% CI 1.15 to 1.54) and exposed more than 5 years ago (RR M2=1.19, 95% CI 1.07 to 1.32) were at greater risk of cognitive impairment (figure 2).

Among men, cognitive impairment was more important for people currently exposed compared with people no longer exposed in different cognitive domains (figure 2). Furthermore, people who were currently exposed had a higher risk of cognitive impairment independently of the duration of exposure (data not shown).

In women, none of the multivariate analyses on delay since last exposure showed any statistical effects.

In regard to demographic differences between the main cohort and the final study population, we performed a sensitivity analysis to evaluate the impact of the exclusion of missing data for covariates and exposure. The associations between solvent exposure and cognitive impairment were consistent after performing multiple imputation for incomplete covariate and solvent data (n=58 235) (data not shown).

Table 3 Association between solvent exposure and global cognitive score (n=41 854)

	Model 1*			Model 2†		
Ref. not exposed	**Coef.**	**95% CI**	**P value**	**Coef.**	**95% CI**	**P value**
Men (n=20 234)						
Types of solvent						
Gasoline for hand washing	**−0.26**	**−0.33 to −0.18**	**<0.0001**	−0.20†*	**−0.28 to −0.12**	**<0.0001**
Trichloroethylene	**−0.16**	**−0.23 to −0.10**	**0.0001**	−0.10	**−0.17 to −0.04**	**0.003**
White spirit	**−0.28**	**−0.34 to −0.19**	**<0.0001**	**−0.21**	**−0.29 to −0.14**	**<0.0001**
Cellulosic thinner	**−0.36**	**−0.46 to −0.26**	**<0.0001**	**−0.30**	**−0.40 to −0.20**	**<0.0001**
No. of type of solvents						
Not exposed	Ref.	–		Ref.	–	
Exposed to one type only	**−0.21**	**−0.29 to −0.14**	**<0.0001**	**−0.17**	**−0.25 to −0.09**	**<0.0001**
Exposed to two different types	**−0.26**	**−0.36 to −0.15**	**<0.0001**	**−0.21**	**−0.31 to −0.10**	**0.0002**
Exposed to 3different types	**−0.27**	**−0.41 to −0.14**	**<0.0001**	**−0.21**	**−0.35 to −0.08**	**0.002**
Exposed to four different types	**−0.41**	**−0.58 to −0.25**	**<0.0001**	**−0.35**	**−0.51 to −0.19**	**<0.0001**
P trend			**<0.0001**			**<0.0001**
Cumulative exposure time						
Not exposed	Ref.	–		Ref.	–	
1–10 years	**−0.13**	**−0.22 to −0.04**	**0.003**	−0.08	−0.17 to 0.01	0.08
10–20 years	**−0.13**	**−0.23 to −0.02**	**0.02**	−0.07	−0.17 to 0.04	0.20
>20 years	**−0.38**	**−0.47 to −0.30**	**<0.0001**	**−0.32**	**−0.41 to −0.23**	**<0.0001**
P trend			**<0.0001**			**<0.0001**
Delay since last exposure						
Not exposed	Ref.	–		Ref.	–	
>5 years	**−0.21**	**−0.27 to −0.14**	**<0.0001**	**−0.15**	**−0.22 to −0.09**	**<0.0001**
<5 years or currently	**−0.38**	**−0.48 to −0.28**	**<0.0001**	**−0.33**	**−0.43 to −0.23**	**<0.0001**
Women (n=21 620)						
Types of solvent						
Gasoline for hand washing	−0.21	−0.43 to 0.01	0.06	−0.15	−0.37 to 0.07	0.19
Trichloroethylene	−0.02	−0.18 to 0.14	0.82	0.03	−0.14 to 0.19	0.73
White spirit	**−0.23**	**−0.42 to −0.04**	**0.02**	**−0.22**	**−0.40 to −0.03**	**0.02**
Cellulosic thinner	0.04	−0.25 to 0.33	0.77	0.11	−0.18 to 0.40	0.71
No. of type of solvents						
Not exposed	Ref.	–		Ref.	–	
Exposed to one type only	**−0.23**	**−0.38 to −0.08**	**0.003**	**−0.18**	**−0.34 to −0.03**	**0.02**
Exposed to two or more different types	0.04	−0.20 to 0.27	0.77	0.06	−0.17 to 0.30	0.59
P trend			0.10			0.28
Cumulative exposure time						
Not exposed	Ref.	–		Ref.	–	
1–10 years	−0.11	−0.31 to 0.08)	0.25	−0.07	−0.27 to 0.12	0.45
>10 years	0.05	−0.21 to 0.32	0.70	0.09	−0.17 to 0.36	0.48
>20 years	**−0.38**	**−0.63 to −0.13**	**0.003**	**−0.31**	**−0.57 to −0.06**	**0.01**
P trend			**0.009**			**0.05**
Delay since last exposure						
Not exposed	Ref.	–		Ref.	–	
>5 years	−0.12	−0.29 to 0.05	0.18	−0.07	−0.24 to 0.10	0.40
<5 years or currently	**−0.21**	**−0.41 to −0.01**	**0.04**	−0.17	−0.37 to 0.03	0.10

*Model 1 adjusted for age, education level, marital status, income, smoking, alcohol consumption, BMI, hypertension, diabetes, cardiovascular disease, respiratory diseases, CESD and FDep09.
†Model 2 adjusted for M1 and night-shift work, repetitive work nd noisy work.
‡The median (IQR) of global cognitive score, from PCA, is 0.08 (−1.02 to 1.15). This is an example of coefficient interpretation for "Coef.=−0.20" for gasoline exposure in model 2, among men: when taking into account all covariates included in model 2, a man, 45–50 years old, has an average global cognitive score of 0.82 compared with 0.62 if exposed. Another example among women, for "Coef=−0.22" interpretation, for white spirit exposure in model 2: a woman, 45–50 years old, has an average global cognitive score of 0.72 compared with 0.50 if exposed.
BMI, body mass index; CESD, Center for Epidemiological Studies–Depression; coef, coefficient; PCA, principal component analysis ; ref, reference.

DISCUSSION

This paper documents the relationship between occupational solvent exposure and cognitive performance in a large sample of middle-aged to early-ageing volunteers (45–69 years old). Men exposed to gasoline, trichloroethylene, white spirit or cellulosic thinner had poorer cognitive performance, even after controlling for individual factors, socioeconomic environment and working conditions. Exposure–effect relationships for the number of solvents and cumulative exposure time were highlighted. Cognitive performance decreased with the number of solvents to which individuals were occupationally exposed and with the cumulative exposure time. Finally, this sample, which included 21 620 women, of whom 550 were exposed to at least one solvent, allowed us to first evidence the detrimental effects of solvents on cognition.

The determinants of cognitive ageing encompass individual characteristics (socioeconomic characteristics, lifestyle, health status, and so on), but also the living environment. The living

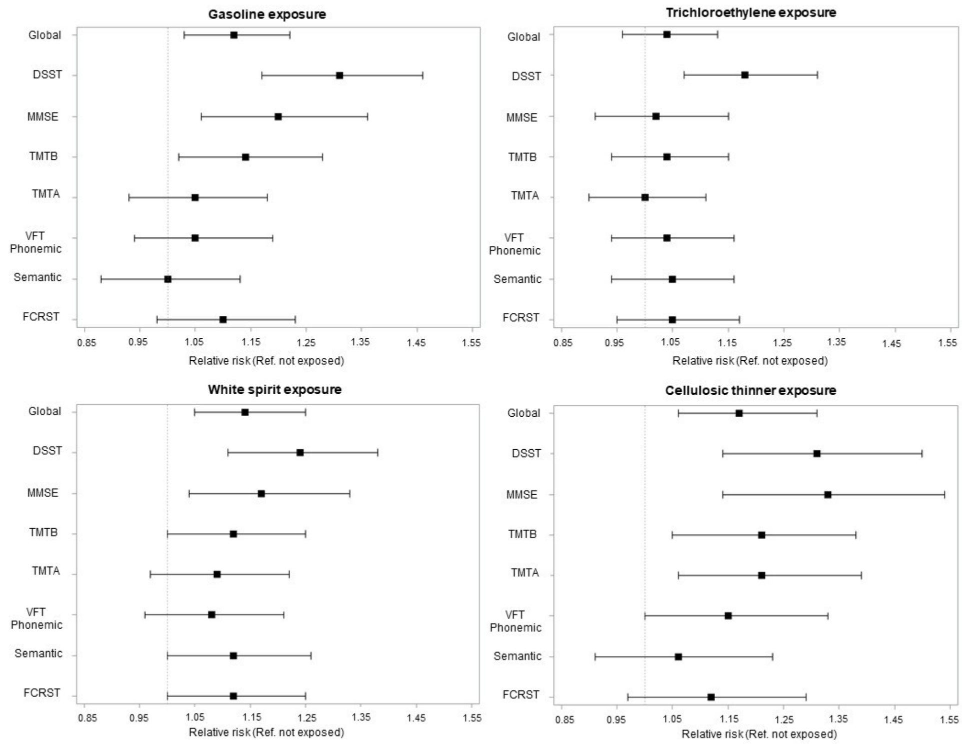

Figure 1 Association between cognitive performances and type of occupational solvent exposure using modified Poisson regression in men (n=20 234) RR, relative risk. For each cognitive score, RRs and their 95% CI were provided by a modified Poisson regression. The RRs estimate the risk of cognitive impairment in participants exposed at each solvents, adjusted for all variables included in model 2 (age, education level, marital status, income, smoking, alcohol consumption, body mass index, hypertension, diabetes, cardiovascular disease, respiratory diseases, Centre for Epidemiological Studies–Depression (CESD) score, French Deprivation Index (FDep09), night-shift work, repetitive work and noisy work). DSST, Digit Symbol Substitution Test; FCRST, Free and Cued Selective Reminding Test; Global, global cognitive score; MMSE, Mini Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Tasks.

conditions influence cognitive performance, both (1) at the collective level with socioeconomic environment and (2) at the individual level with working conditions. Living in deprived neighbourhood is associated with poorer cognitive performance and higher risk of dementia.[29] In addition, performing a job with working conditions such as shift work[30 31] or noise exposure[32–34] is conditions associated with lower cognitive performance.

Nevertheless, the effects on cognition of joint exposures to solvents and working conditions are currently poorly understood. After adjustment for working environment in addition to classic confounders and socioeconomic environment, most of the associations between solvent exposure and cognitive performance remained significant. However, they weakened, particularly in women, showing the importance of taking into account other working conditions when studying a chemical occupational exposure. The study of the impact of working environment on health should be considered with a larger overview of its complexity.

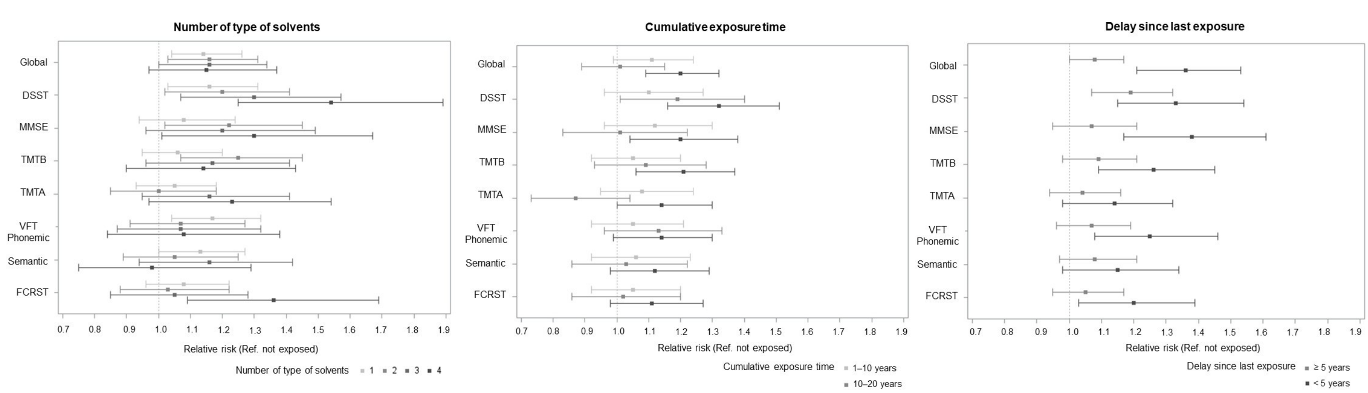

Figure 2 Association between cognitive performances and number of solvent type exposure, cumulative exposure time and delay since last exposure using modified Poisson regression in men (n=20 234). RR, relative risk. The RRs estimate the risk of cognitive impairment in participants exposed at each solvents, adjusted for all variables included in model 2 (age, education level, marital status, income, smoking, alcohol consumption, body mass index, hypertension, diabetes, cardiovascular disease, respiratory diseases, Centre for Epidemiological Studies–Depression (CESD) score, French Deprivation Index (FDep09), night-shift work, repetitive work and noisy work). DSST, Digit Symbol Substitution Test; FCRST, Free and Cued Selective Reminding Test; Global, global cognitive score; MMSE, Mini Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Tasks.

Among men, we found significant associations between solvent exposure and measures of global cognitive function, episodic verbal memory, delayed recall, attention, psychomotor speed and executive function and marginal association with fluency. Our findings are in line with those previously reported in occupational cohorts, mainly showing detrimental effect in the areas of processing speed and attention.[9] Our results are also in agreement with those from the prospective cohort of French national gas and electricity (GAZEL) employees (n=2143 men)[6] or from the prospective Netherlands cohort study (n=2411 men).[35] The consistent associations found for the DSST score are particularly interesting because this cognitive test is likely to be one of the most appropriate to examine cognitive performance in younger persons; it is a sensitive test[36] requiring sustained attention, processing speed and visual spatial skills, and poor performance on this test has been linked to incident dementia.[37]

Subjects who were not exposed or not exposed in the 5 years before cognitive testing had a lower risk compared with those still exposed. These findings suggest that cognitive impairment linked to solvent exposure may lessen as the time since exposure increases, suggesting a potential reversibility.[8] However, some studies suggest that high chronic exposure can be associated with permanent cognitive changes[38 39] and persist after retirement.[38] Our findings were not modified by retirement status (data not shown).

Unlike other studies, this study examined the association between lifetime occupational exposure to solvents and cognitive functioning in a large sample from the general population, in participants older than 45 years of age and with the opportunity to study both men and women. We adjusted our analyses for multiple covariates. The strengths of this study also include the use of different statistical approaches (linear regression, modified Poisson regression) and sensitivity analyses. Our results were confirmed for multiple cognitive domains as well as a global cognitive score. Furthermore, cognitive performances were evaluated by a battery of tests under standardised conditions by trained neuropsychologists and the cut-offs of impaired cognition were established from norms stratified on sex, age and education.

Major limitation of this study is the evaluation of solvent exposure. Solvent exposure was self-reported (with only four categories of solvents) and retrospective data collection may be influenced by current cognitive function. We did not have access to detailed exposure levels or occupational tasks leading to exposure; however, the dose–effect relationships are in favour of the plausibility of associations. At this stage, only baseline cognitive assessment was available, so these results from cross-sectional analyses should be confirmed in further longitudinal analyses on cognitive decline and incident dementia. Furthermore, in view of the differences in characteristics between the individuals included and not in the analyses, we cannot exclude a potential selection bias that may underestimate the associations highlighted. However, association between solvent exposure and cognitive impairment remains significant after using multiple imputation for incomplete covariate and solvent data (data not shown). As in previous studies, we were unable to take into account home exposures to solvents; this could underestimate the exposure of women in the context of domestic chores. Furthermore, protection equipment vary across occupations and according to company size and period, and they were not considered. We examined the role of the number of solvents types because they may have synergistic or antagonistic effects, and this issue has been little investigated.[9] However, the combinations that we defined were not precise enough for this and did not take into account all the possible interactions between the different types of solvents or with other potential neurotoxicants, such as heavy metals and pesticides. Moreover, even if this sample was large, showing associations in women remains difficult because of their limited exposure. The potential sex differences could be explained in part not only by differences in prevalence of exposure but also by differences in the metabolism of solvents that could influence the toxicokinetics of the solvents.[40]

These findings strengthen the evidence in favour of detrimental effects of solvents on cognitive health by showing that occupational solvent exposure is associated with poorer cognitive performance, independently of individual characteristics and working environment. Associations were mainly highlighted in men besides first evidence of solvent detrimental effect on cognition in women was shown.

Acknowledgements The authors thank the 'Caisse nationale d'assurance maladie' (CNAM), the 'Centres d'Examen de Sante' of the French Social Security which are collected a large part of the data, and all the CONSTANCES' volunteers without which this study will not be possible.

Contributors NL performed the statistical analysis, interpreted the results and edited the first draft of the manuscript. GC and FA also contributed to the statistical analysis. MG and MZ acquired the data. CB obtained funding, designed the study, contributed data and helped to write the manuscript. CB and AE developed study hypotheses. All authors critically revised the manuscript.

Funding The CONSTANCES cohort study was supported and funded by the 'Caisse nationale d'assurance maladie' (CNAM). The CONSTANCES cohort study is an 'Infrastructure nationale en Biologie et Santé' and benefits from a grant from Agence Nationale de la Recherche (ANR-11-INBS-0002). CONSTANCES is also partly funded by MSD, AstraZeneca and Lundbeck. The present analyses were supported by a grant from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, EST – No. 2016/1/102).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The CONSTANCES cohort received ethical approval from the French National Data Protection Authority (authorisation no. 910486) and the Institutional Review Board of the National Institute for Medical Research (authorisation no. 01-011). All participants gave informed consent to participate.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Anonymised data will be shared by request to the CONSTANCES scientific committee.

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