Occupational solvent exposure and cognition

Does the association vary by level of education?

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ABSTRACT

Objective: Chronic occupational solvent exposure is associated with long-term cognitive deficits. Cognitive reserve may protect solvent-exposed workers from cognitive impairment. We tested whether the association between chronic solvent exposure and cognition varied by educational attainment, a proxy for cognitive reserve.

Methods: Data were drawn from a prospective cohort of French national gas and electricity (GAZEL) employees (n = 4,134). Lifetime exposure to 4 solvent types (chlorinated solvents, petroleum solvents, benzene, and nonbenzene aromatic solvents) was assessed using a validated job-exposure matrix. Education was dichotomized at less than secondary school or below. Cognitive impairment was defined as scoring below the 25th percentile on the Digit Symbol Substitution Test at mean age 59 (SD 2.8; 88% of participants were retired at testing). Log-binomial regression was used to model risk ratios (RRs) for poor cognition as predicted by solvent exposure, stratified by education and adjusted for sociodemographic and behavioral factors.

Results: Solvent exposure rates were higher among less-educated patients. Within this group, there was a dose-response relationship between lifetime exposure to each solvent type and RR for poor cognition (e.g., for high exposure to benzene, RR = 1.24, 95% confidence interval 1.09–1.41), with significant linear trends ($p < 0.05$) in 3 out of 4 solvent types. Recency of solvent exposure also predicted worse cognition among less-educated patients. Among those with secondary education or higher, there was no significant or near-significant relationship between any quantification of solvent exposure and cognition.

Conclusions: Solvent exposure is associated with poor cognition only among less-educated individuals. Higher cognitive reserve in the more-educated group may explain this finding. ***Neurology***® **2012;78:1754–1760**

GLOSSARY

CI = confidence interval; **DSST** = Digit Symbol Substitution Test; **JEM** = job exposure matrix; **MMSE** = Mini-Mental State Examination; **RR** = risk ratio.

Occupational exposure to organic solvents is a risk factor for cognitive impairment.[1–3] Solvents, classifiable as chlorinated, petroleum, benzene, and nonbenzene aromatic, are used in painting, degreasing, pesticides, and adhesives, and are common occupational exposures, with exposure prevalence estimated to be 8% in working populations in industrialized countries.[4] Solvents affect CNS functioning (chronic toxic encephalopathy), including attention, processing speed, and motor performance.[5,6] If exposure is low, memory and concentration problems may attenuate or fail to progress when exposure ceases.[7,8] However, sustained motor/attention difficulties and intellectual impairment have been observed among the highly exposed. Acute cases may progress to permanent neurologic deficits, although symptoms may lessen with time since exposure.[4,6,9]

There is a body of research into neurotoxic effects of solvents, but gaps remain. Little is known about potential effect modifiers of occupational solvent exposure. Education is a modifier of partic-

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ular interest because of evidence of its role in shaping cognitive reserve, the ability of the brain to withstand insults and continue normal functioning.[10–12] Two prior studies found an association between occupational lead exposure and cognition only among those with poor cognitive reserve, as defined by measures of reading achievement.[13,14] However, this relationship has not been tested for other exposures or in retired populations.

The objective of this study was to examine whether effects of occupational solvent exposure on cognition vary by educational attainment. We hypothesized that risks associated with solvent exposure would be greater among those with less education than those with more education. We also examined whether differences were attributable to more recent exposure among the less-educated.

METHODS

Population. The present study was conducted within the GAZEL prospective cohort, established in 1989 among employees of the French national gas and electric company as described elsewhere.[15] Of 20,625 members of the original cohort, 10,537 were eligible (aged ≥55) for physical and cognitive examinations conducted from 2002 to 2004. Of those invited, 5,377 (51%) participated and had valid cognitive scores. Those who declined participation were statistically but not substantively younger than participants (mean birth year = 1944.1 vs 1944.0, respectively, p for difference = 0.004) and were not significantly different by educational attainment ($p = 0.81$) or occupational grade at 35 ($p = 0.14$). After excluding women (n = 1,181) due to very low exposure (<5% prevalence of high exposure to solvents), men missing chemical exposure data (n = 53), and educational attainment data (n = 9), 4,134 individuals were included.

Outcome. The Digit Symbol Substitution Test (DSST), a subscale of the Wechsler Adult Intelligence Scale, measures executive function and psychomotor speed.[16] DSST has demonstrated sensitivity to subpathologic cognitive difficulties in relatively young, healthy populations. Furthermore, a meta-analysis suggests that the association between age and performance on the DSST is not significantly different for more- and less-educated individuals.[17] Although participants also completed the Mini-Mental State Examination (MMSE),[18] strong ceiling effects in the present population made that test unsuitable. Substantively, DSST was best suited for the present analysis based on evidence that solvent exposure affects motor speed, attention, and processing speed, domains captured by DSST.[6] In the present analyses, individuals scoring at or below the 25th percentile of the sample distribution were classified as "impaired."

Exposures. A validated job exposure matrix (JEM) was used to characterize inhaled exposure to 4 solvent categories: chlorinated solvents (tetrachloromethane, trichloroethylene, perchloroethylene, dichloromethane, trichloroethane); petroleum solvents (hydrazine); benzene; and nonbenzene aromatic solvents (toluene diisocyanate).[19] JEMs are a series of tables in which exposures are listed on 1 axis and job titles on the other, with titles grouped to maximize homogeneity of exposure; table cells contain either semiquantitative (exposed/unexposed) or quantitative (dose, time-weighted average, or probability) estimates of exposure.[20,21] Tables for different time periods report how exposure for a given job title varied across time and also permit reconstruction of workers' cumulative exposure across their careers. Exposure estimates in the present matrix (MATEX) were derived retrospectively by experts, using records from ongoing industrial hygiene monitoring of employee workstations and occupational medicine data from the company, to extrapolate from observed workers to those in similar positions.[22] Cumulative exposure to each solvent type in this analysis was calculated as a weighted sum for every year (dose multiplied by probability of exposure) based on job title, from date of hire until end of data collection in 1998. Job titles were extracted from company records. Individuals were first classified as ever/never exposed to each class of solvents; exposed individuals were then dichotomized by 1) total dose (below population median for lifetime dose among the exposed equaled low exposure; at or above median equaled high exposure) and 2) year of most recent exposure (between 1960 and 1979 was distal exposure; 1980 to 1998 was proximal). MATEX data collection and modeling ended in 1998 because most GAZEL participants had either retired (43%) or advanced out of high-exposure jobs. Workers were generally employed at the company from career inception to retirement; thus, total career exposure to organic solvents could be modeled with greater precision than estimates from a population-based JEM modeling exposure across multiple companies.[20,22]

Individuals self-reported highest educational attainment at study baseline (1989) in 8 categories, dichotomized into less-educated (primary school, middle/lower secondary school; n = 2,412) and more-educated (high school diploma, university, professional certification, advanced technical certification; n = 1,722).

Covariates. Covariates included in analyses included age (in years) at cognitive assessment, occupational grade at age 35 (reported in EDF-GDF company records; classified as executive, skilled professional including foremen, unskilled nonmanual, and unskilled manual) weekly alcohol consumption (0, 1–14, 15–27, >27 units, corresponding to abstainer, light, moderate, and heavy drinking), and smoking status (smoker vs nonsmoker) assessed in 2003. We measured occupational grade at age 35 because many EDF-GDF employees are promoted shortly before retirement; thus, a midcareer measure better captures lifetime position. Missing values (n = 116 for smoking, n = 28 for alcohol) were replaced with modal values.

Analyses. Within each educational group, we used log-binomial regression to calculate the risk ratio (RR) of cognitive impairment associated with solvent exposure (none, low, or high exposure). We adjusted first for known sociodemographic risk factors for cognitive impairment (age and occupational grade) and in subsequent models adjusted for behavioral risk factors (smoking and alcohol use).

We tested for linear trend for poor cognition by exposure level (none, low, high), but because of some evidence of nonlinearity or threshold effects, we report RRs for each exposure level. Because models are logarithmic and therefore multiplicative rather than additive, we tested for statistical interaction between solvent exposure and education on the multiplicative scale using interaction terms in regression models, assessing whether RRs associated with exposure differed by educational status. We also conducted sensitivity analyses to test effects of dose and edu-

cation on continuous, rather than dichotomous, DSST score; results are not reported here but are available upon request.

The effects of solvents on cognition are thought to attenuate with time since last exposure.[23] One possible explanation for different associations between solvent exposure and cognitive impairment by educational status is that education enabled respondents to move out of high-exposure jobs earlier in their careers. The less-educated may therefore have been more recently exposed to solvents than the more-educated, in addition to having higher cumulative exposure levels. We thus tested whether education confounded the association between time since last solvent exposure and cognition, estimating associations between time since last exposure and cognition with and without adjustment for education. Next, to test for effect modification, we stratified analyses by educational attainment and tested for homogeneity of effect estimates across strata. We also tested for statistical interaction between education and time since last exposure. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Table 1 Distribution of exposure variables, for whole population and by educational attainment

	All participants (n = 4,134)	Less-educated (n = 2,412)	More-educated (n = 1,722)
Age at screening, y			
55–59	2,213 (53.53)	1,318 (54.64)	895 (51.97)
60–63	1,921 (46.47)	1,094 (45.36)	827 (48.03)
Occupational grade at age 35 y			
Executive	739 (17.88)	63 (2.61)	676 (39.26)
Professional	2,449 (59.25)	1,569 (65.08)	880 (51.10)
Nonmanual	198 (4.79)	128 (5.31)	70 (4.07)
Manual	747 (17.88)	651 (27.00)	96 (5.57)
Chlorinated solvent exposure			
Not exposed	2,582 (62.46)	1,197 (49.63)	1,384 (80.37)
Exposure level (in exposed)			
Low	773 (18.70)	567 (23.51)	206 (11.96)
High	780 (18.87)	648 (26.87)	132 (7.67)
Last exposure (in exposed)			
Last exposed pre-1980	727 (17.59)	518 (21.48)	209 (12.14)
Last exposed 1980 onwards	825 (19.96)	696 (28.86)	129 (7.49)
Petroleum solvent exposure			
Not exposed	2,943 (71.19)	1,533 (63.56)	1,410 (81.88)
Exposure level (in exposed)			
Low	589 (14.25)	385 (15.96)	204 (11.85)
High	602 (14.56)	494 (20.48)	108 (6.27)
Last exposure (in exposed)			
Last exposed pre-1980	845 (20.44)	590 (24.46)	255 (14.81)
Last exposed 1980 onwards	334 (8.32)	288 (11.94)	56 (3.25)
Benzene exposure			
Not exposed	2,882 (69.71)	1,487 (61.65)	1,395 (81.01)
Exposure level (in exposed)			
Low	626 (15.14)	413 (17.12)	213 (12.37)
High	626 (15.14)	512 (21.23)	114 (6.62)
Last exposure (in exposed)			
Last exposed pre-1980	845 (20.44)	593 (24.59)	252 (14.63)
Last exposed 1980 onwards	407 (9.85)	332 (13.76)	75 (4.36)
Nonbenzene aromatic solvents			
Not exposed	4,003 (96.83)	2,324 (96.35)	1,679 (97.50)
Exposure level (in exposed)			
Low	65 (1.57)	38 (1.58)	27 (1.57)
High	66 (1.60)	50 (2.07)	16 (0.93)
Last exposure (in exposed)			
Last exposed pre-1980	103 (2.49)	67 (2.78)	36 (2.09)
Last exposed 1980 onwards	28 (0.68)	21 (0.87)	7 (0.41)

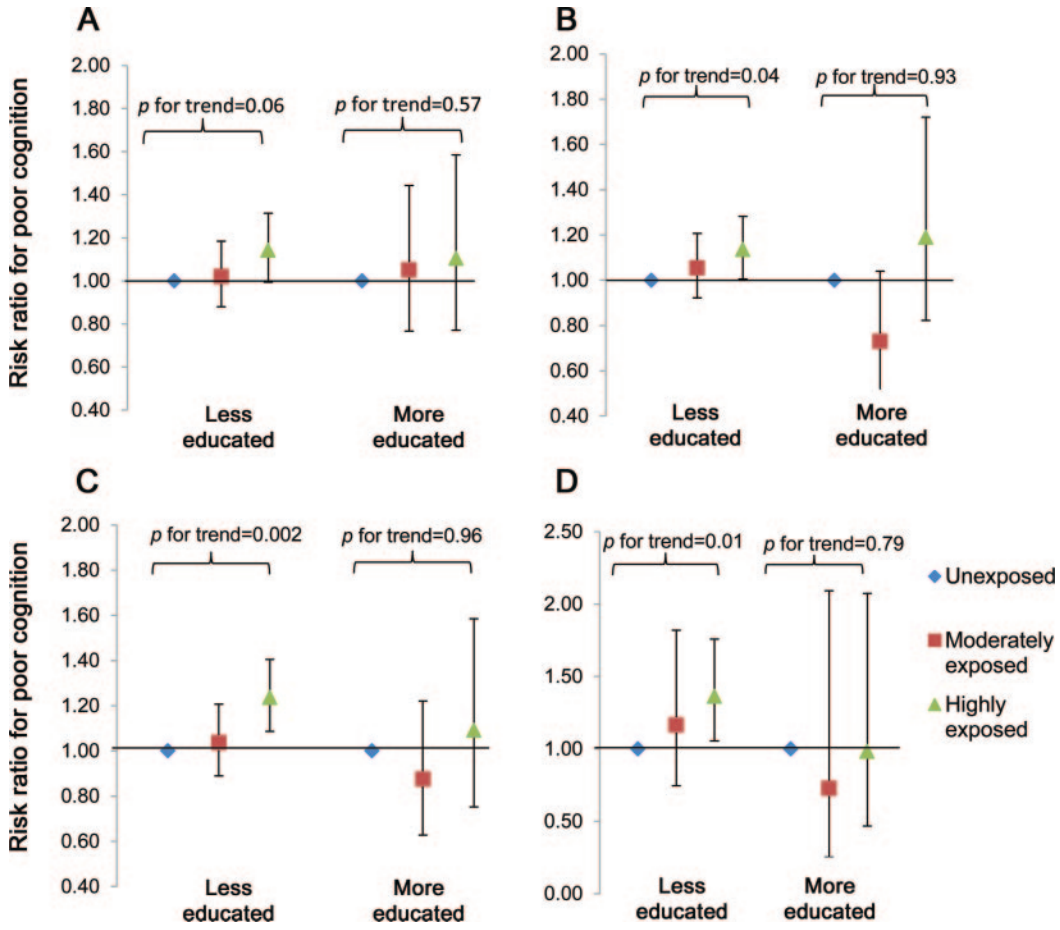
Standard protocol approvals, registrations, and patient consents. Approval for the GAZEL cohort was obtained by the French national committee for data privacy (Commission Nationale Informatique et Libertés); our study was conducted with the approval of the human subjects committee at INSERM. Written informed consent was provided by all GAZEL participants at cohort inception (1989) and cognitive testing (2002–2004).

RESULTS DSST was completed by 4,134 men, with mean score of 48.86 (SD 9.61, range 5–93; cutoff score for "impaired" was ≤41). Mean age at testing, in 2002–2004, was 59; 58% reported low educational attainment (table 1). Among the less-educated, 32% (n = 765) were cognitively impaired, compared with 16% (n = 273) of more-educated participants. Ninety-one percent (n = 3,747) retired prior to cognitive testing. Among those not retired (n = 387), 8% (n = 33) were exposed to any solvent between 1990 and 1998, when exposure assessment ended.

Respondents with secondary education or higher were systematically less likely than those with subsecondary attainment to have any exposure to chlorinated solvents (20% vs 50%), petroleum solvents (18% vs 36%), benzene (19% vs 38%), or nonbenzene aromatic solvents (2% vs 4%; table 1). Among the exposed, in both high- and low-education groups, fewer people were exposed in latter parts of the follow-up period (1980–1998) than the former (1960–1979).

Among the less-educated, in fully adjusted models accounting for age, occupational grade, alcohol consumption, and smoking, RR for cognitive impairment was greater among those highly exposed to each of 4 solvent types, compared with unexposed: chlorinated solvents (RR = 1.14; 95% confidence interval [CI] 0.99, 1.31), petroleum solvents (RR = 1.14; 95% CI 1.01, 1.28), benzene (RR = 1.24; 95% CI 1.09, 1.41), and nonbenzene aromatic solvents (RR = 1.36; 95% CI 1.06, 1.76) (RRs displayed graphically in the figure). Point estimates showed a dose trend, and trend tests indicated significant or near-significant dose-response relations between each solvent type and cognition: chlorinated solvents (p for trend = 0.06), petroleum solvents

Figure Risk ratio for poor cognition by educational attainment and solvent exposure status



Fully adjusted risk ratio (95% confidence interval) for poor cognitive function as predicted by lifetime cumulative exposure to 4 classes of organic solvents, stratified by educational attainment. *p* Values are for linear trend within educational strata. These figures indicate the differential effects of solvent exposure on cognitive function in less-educated vs more-educated individuals. (A) Cumulative chlorinated solvent exposure. (B) Cumulative petroleum solvent exposure. (C) Cumulative benzene exposure. (D) Cumulative nonbenzene aromatic solvent exposure.

($p = 0.04$), benzene ($p = 0.002$), and nonbenzene aromatic solvents ($p = 0.01$) (table 2).

Among the more-educated, in fully adjusted models, we observed no statistically significant associations between high solvent exposure and cognitive impairment, and no significant linear trends between exposure dose and cognitive impairment for any solvent type: chlorinated solvents (RR for high exposure = 1.11; 95% CI 0.77, 1.58; p for trend = 0.57), petroleum solvents (RR = 1.19; 95% CI 0.82, 1.72; $p = 0.93$), benzene (RR = 1.09; 95% CI 0.75, 1.58; $p = 0.96$), or nonbenzene aromatic solvents (RR = 0.98; 95% CI 0.47, 2.07; $p = 0.80$). All associations between low exposure and cognition were nonsignificant.

Tests of interaction between education and exposure intensity of individual solvents on cognitive impairment were not statistically significant ($p = 0.24$ for chlorinated solvents, $p = 0.94$ for petroleum solvents, $p = 0.21$ for benzene, $p = 0.52$ for nonbenzene aromatic solvents) (results not shown).

To test whether the above pattern was attributable to differential time since last exposure in more-educated vs less-educated individuals, we first analyzed effects of time since last exposure among all participants, by solvent type, adjusting first for sociodemographic and behavioral risk factors and then for the preceding factors plus education. We found a dose-response relationship between time since last exposure and cognition in the whole population, with the most proximally exposed experiencing significantly worse cognition than unexposed in all categories except nonbenzene aromatic solvents. Tests of interaction between time since exposure and education were not statistically significant ($p > 0.05$).

Upon stratifying by education, among the less-educated there remained a general trend of poorer cognition among the more recently exposed. For

Table 2 Association between solvent exposure and cognition, for whole population and by educational attainment[a]

	All participants, RR (95% CI)	All participants, education-adjusted, RR (95% CI)	Less-educated participants, RR (95% CI)	More-educated participants, RR (95% CI)
Chlorinated solvents				
Unexposed	1.0	1.0	1.0	1.0
Last exposed pre-1980	1.08 (0.94, 1.24)	1.05 (0.91, 1.20)	1.06 (0.91, 1.23)	1.00 (0.72, 1.39)
Last exposed 1980 onwards	1.19 (1.04, 1.36)	1.11 (0.97, 1.27)	1.10 (0.96, 1.27)	1.24 (0.86, 1.78)
p For trend	0.02	0.13	0.18	0.32
Petroleum solvents				
Unexposed	1.0	1.0	1.0	1.0
Last exposed pre-1980	1.09 (0.96, 1.22)	1.07 (0.95, 1.20)	1.10 (0.97, 1.25)	0.90 (0.67, 1.22)
Last exposed 1980 onwards	1.17 (1.01, 1.36)	1.14 (0.98, 1.32)	1.17 (1.00, 1.37)	0.93 (0.56, 1.56)
p For trend	0.03	0.07	0.03	0.55
Benzene				
Unexposed	1.0	1.0	1.0	1.0
Last exposed pre-1980	1.13 (1.00, 1.27)	1.11 (0.98, 1.24)	1.13 (1.00, 1.29)	1.00 (0.75, 1.35)
Last exposed 1980 onwards	1.19 (1.03, 1.38)	1.16 (1.01, 1.34)	1.21 (1.04, 1.40)	0.89 (0.55, 1.45)
p For trend	0.007	0.02	0.008	0.76
Nonbenzene aromatic solvents				
Unexposed	1.0	1.0	1.0	1.0
Last exposed pre-1980	1.30 (1.03, 1.63)	1.32 (1.06, 1.64)	1.40 (1.14, 1.73)	0.86 (0.42, 1.78)
Last exposed 1980 onwards	0.91 (0.52, 1.59)	0.91 (0.52, 1.57)	0.86 (0.45, 1.64)	1.20 (0.39, 3.65)
p For trend	0.30	0.26	0.18	0.95

Abbreviations: CI = confidence interval; RR = risk ratio.
[a] Analysis adjusted for occupational grade at age 35 years and age, smoking status, and alcohol consumption.

chlorinated solvents the RR for recent exposure was 1.10 (95% CI 0.96, 1.27), for petroleum solvents RR was 1.17 (95% CI 1.00, 1.37), for benzene RR was 1.21 (95% CI 1.04, 1.40), and for nonbenzene aromatic solvents RR was 0.86 (95% CI 0.45, 1.64). Test for linear trend of cognitive impairment by time since exposure was not significant for chlorinated and aromatic solvents ($p = 0.18$ for both) but was significant for petroleum solvents and benzene ($p = 0.03$ and 0.01, respectively). Among the more-educated, recent exposure to any solvent type was not significantly associated with poor cognition, and with no evidence of a linear trend.

DISCUSSION In French utility workers, lifetime solvent exposure is associated with cognitive function after age 55.[9] The present study tested whether the relationship between solvent exposure and cognition varied by educational attainment. We found that, among less-educated workers, RR for poor cognition was significantly higher among those with high lifetime solvent dose. The risk was also higher among less-educated workers with recent exposure. Additionally, there was a dose-response relationship between both exposure metrics and cognition. Conversely, among more-educated workers, solvent exposure was not associated with cognitive deficits, in analyses taking into account first total lifetime dose and then time since last exposure. In analyses testing for effects of time since last exposure on cognition, proximal exposure was generally associated with poor cognition among less-educated but not among more-educated workers. However, formal tests of effect modification on the multiplicative scale between education and exposure measures were not statistically significant.

The analysis has several limitations. There is risk of selection into the exposed group with respect to the outcome, if individuals with poorer cognition tend to stay in higher-exposed (e.g., low-wage) jobs rather than being promoted out of such positions. We have a single cognitive assessment that was taken after the exposure period ended, so we are unable to test for this possibility. We partially addressed this concern by controlling for occupational grade at age 35, because the most talented or motivated individuals who started in low-level positions (average age at hire was 22) were likely to be promoted to managerial roles by 35. However, repeat assessments of cognitive function would have permitted a more

thorough investigation of causal ordering and potential selection bias into the exposed group. Using a job-exposure matrix to assess exposure to solvents, as we did, permits extensive exposure assessment while eliminating risk of differential misclassification of exposure with respect to the outcome.[24] However, because the exposure assessments are models rather than direct measurements, there is risk of nondifferential misclassification. Potential misclassification is reduced in matrices such as MATEX that are constructed for a particular company or industry. Such misclassifications would generally bias results toward the null or flatten exposure-response curves,[25] and would not be differential with respect to the outcome or to education.[21,26] Another weakness is that education is an imperfect proxy for cognitive reserve and both educational attainment and adult cognitive function can be a common effect of childhood intelligence or early-life social conditions.[27] We only tested associations with 1 cognitive measure (DSST), which was reasonable given the close alignment between hypothesized effects of solvents and the domains tested by DSST. Finally, in the highly educated subgroup there is low prevalence of both high exposure and proximal exposure to all types of solvents, perhaps reducing power to detect an association, as indicated by the relatively wide CIs for more-educated workers in the figure. This may also explain the nonsignificance of our tests for statistical interaction.

The analysis also has several strengths. First, we conducted the study in a population in which individuals with varying levels of educational attainment are exposed to chemicals throughout working life and are allowed to advance professionally without being highly educated. Because education (and thus lack of sustained occupational chemical exposure) is almost always associated with more skilled, white-collar work, GAZEL affords a unique opportunity to look at joint effects of education and solvent exposure on cognition. From a methodologic standpoint, our study was strengthened by use of a validated exposure assessment tool enabling quantification of dose, exposure period, and duration of exposure for all major solvent types in a large working population. Exposure was also prospectively assessed based on employment records of job type, precluding recall bias that was a weakness of previous case-control studies of the solvent-cognition relationship.

There are 2 potential causal explanations why solvent exposure has a stronger effect on cognition among less-educated compared with more-educated people. First, individuals with more education may better protect themselves against adverse exposures; thus, while exposure as measured by job titles might be similar across education levels, actual dose is lower among the better educated. However, this scenario is unlikely because the matrix already takes into account discrepancies between exposure and dose within and across occupational grades, and we additionally adjusted for grade. The other causal explanation, which has been proposed for lead exposure but never to our knowledge for solvents or other neurotoxic agents, is that the denser neural network associated with education (cognitive reserve) masked or delayed expression of physiologic changes in the brain secondary to solvent exposure. This hypothesis is consistent with research showing that education modifies the association between neuroimaging markers of disease, such as white matter hyperintensities[28] and neuritic and diffuse plaques,[29] and performance on cognitive tests.

The latter explanation for the findings is of particular interest because it suggests that early-life interventions to improve quality and quantity of education could protect cognitive function in later life, not only by permitting individuals to select out of future high-exposure settings, but also by providing more-educated individuals with a buffer against effects of such exposures should they occur. However, the results should not be interpreted to mean that an educated workforce obviates the need for workplace personal protective equipment or administrative controls against occupational hazards. Rather, they suggest that upfront investment in education can serve as a broad shield against both known and unknown neurotoxic exposures across the life course. This is especially salient given evidence that the federally mandated Occupational Health and Safety Administration permissible exposure limit in the United States for some solvents may be insufficient to protect workers against health consequences of exposure.[30]

While we hypothesize that greater cognitive reserve in the more-educated group is partially responsible for the observed effect, this study constitutes preliminary rather than definitive evidence. Future research could explore whether this differential effect of solvents on cognition exists for other factors across the life course thought to create or deplete reserve, such as intelligence, occupational attainment, health behaviors, stress, and social activities.[31,32] Additionally, testing of whether this relationship also exists for other occupational neurotoxic exposures such as manganese or pesticides[3] would improve understanding of the mechanism at play. Our study suggests that social disadvantage early in life may be exacerbated by greater vulnerability to occupational exposures, in turn leading to disparities in cognitive function in early old age.

AUTHOR CONTRIBUTIONS

Dr. Sabbath co-generated the hypothesis, performed statistical analyses, and drafted the manuscript. Dr. Glymour helped develop the hypothesis and analytical plan, provided ongoing methodologic support, and edited the manuscript. Dr. Berr helped generate the hypothesis, provided exper-

tise on the solvent-cognition association, and edited the manuscript. Dr. Singh-Manoux provided input on previous versions of this analysis and edited the manuscript. Dr. Zins co-directs the GAZEL cohort, provided ongoing guidance, and edited the manuscript. Dr. Goldberg co-oversaw the analytic process, co-directs the GAZEL cohort, and edited the manuscript. Dr. Berkman helped develop the hypothesis, co-oversaw the analytic process, and edited the manuscript.

DISCLOSURE

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