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Exposure to Secondhand Smoke and Cognitive Function Among Middle-aged and Older Women in China: Findings of 3-waves of the China Health and Retirement Longitudinal Study

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Title

Exposure to Secondhand Smoke and Cognitive Function Among
Middle-aged and Older Women in China: Findings of 3-waves
of the China Health and Retirement Longitudinal Study

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Abstract

Objectives: To examine the association between passive smoking and women's global cognitive function and cognitive subdomains.

Design: Cohort study

Participants: Data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS), and panel data analysis was applied to wave 1 and wave 2 (2011–2013), wave 2 and wave 3 (2013–2015) and wave 1 and wave 3 (2011–2015). Data from a total of 6875 Chinese women were selected for analysis, including 2981 who were interviewed in 2011, 2471 in 2013, and 1894 in 2015.

Primary and secondary outcome measures:

Global cognitive function, domains of cognitive function including visuospatial ability, orientation and attention, and episodic memory could be assessed by various sections of CHARLS questionnaire.

Results: Passive smoking was found to be significantly associated with cognitive function. Compared with those had not been exposed to household secondhand smoking, women who had lived with a smoking husband for over 40

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4 years had significantly faster cognition decline,
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6 especially in visuospatial ability(95%CI, -0.08--0.01 P <
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8 0.05) and episodic memory function(95%CI, -0.31-- -0.01 P =
9
10 0.031). In addition, compared with individuals with lower
11
12 educational levels, and residing in rural area, those
13
14 with more education or living in urban area had higher
15
16 cognitive scores, although exposed to SHS.
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22 **Conclusions:** Passive smoking within households is a risk
23
24 factor for cognitive decline among Chinese non-smoking
25
26 women. Provision of more educational opportunities and
27
28 screening for depressive symptoms in advance for Chinese
29
30 women should be promoted, as these will also help to
31
32 protect them against the negative effects brought on by
33
34 passive smoking.
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40 **Key words:** aging; passive smoking; panel analysis;
41
42 visuospatial ability; memory
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44

45 **Strengths and limitations of this study:**
46

- 47
48 ➤ The first study to investigate on the association
49
50 between secondhand smoke exposure and women's different
51
52 domains of cognitive functions in China using a 4-year
53
54 longitudinal national representative data.
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57
58 ➤ Addressed the issue of reverse causation in observational cohort studies by used
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4 lagged dependent variable models and adjust for baseline cognition scores
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7 ➤ The exposure to secondhand smoke was evaluated based on
8
9 self-report measures.
10
11 ➤ The analyses only contained household SHS exposure and
12
13 excluding environmental exposure.
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38 **Introduction**

39
40 China's population has been ageing rapidly. By 2050,
41
42 there will be 400 million Chinese citizens aged over 65
43
44 years old, and 150 million of whom will be older than 80
45
46 years old(Fang, Scheibye-Knudsen et al. 2015), which
47
48 brought about formidable healthcare challenges. It will
49
50 become increasingly important to understand the cognitive
51
52 changes that accompany aging, both normally and
53
54 pathologically(Harada, Natelson Love et al. 2013).
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4 Cognitive impairment, described as a decline in
5
6 intellectual functions (Robertson, Savva et al. 2013),
7
8 ranges from mild forms of forgetfulness to severe and
9
10 debilitating dementia and is common among the elderly (Yin,
11
12 Ma et al. 2016). The prevalence of cognitive impairment is
13
14 rising, with national figures estimating that around 9% of
15
16 older persons in China had cognitive impairment in 2011 (Yin,
17
18 Ma et al. 2016).

19
20 Numerous determinants such as environmental, individual,
21
22 and genetic factors could favor evolution toward cognitive
23
24 impairment, and both age and late-life hypertension
25
26 increase the risk of dementia over time (Bernardin, Maheut-
27
28 Bosser et al. 2014). The mechanism lies in age-related
29
30 functional and structural changes in cerebrovascular small
31
32 and large blood vessels (Tadic, Cuspidi et al. 2016).
33
34 Besides chronic diseases factors, depression has long been
35
36 known to affect memory and other neurocognitive domains,
37
38 and be associated with an increased risk of developing mild
39
40 cognitive impairment (MCI) in cognitively normal elderly
41
42 people (Taivalantti, Barnett et al. 2019).

43
44 Passive smoking is a heated public health issue in China.
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46 Exposure to secondhand smoke (SHS), also known as "passive
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4 smoking," refers to a situation where a non-smoker inhales
5
6 another person's smoke either by exposure to side stream
7
8 smoke or mainstream smoke (Ling and Heffernan 2016). Current
9
10 smoking prevalence in China decreased from 31.1% in 2002
11
12 to 28.1% in 2010; however, the number of adults exposed to
13
14 secondhand smoking during this period still increased from
15
16 540 million to 556 million (Harada, Natelson Love et al.
17
18 2013). The negative health effects of high levels of
19
20 exposure to SHS may be close to those of active smoking,
21
22 including inferior performance on measures of general
23
24 intelligence, visuospatial learning and memory and fine
25
26 motor dexterity (Durazzo, Meyerhoff et al. 2012). Given the
27
28 association between exposure to SHS and risk factors for
29
30 cognitive impairment such as cardiovascular disease (Teo,
31
32 Ounpuu et al. 2006), hypertension (Kim, 2019), and stroke
33
34 (Malek, 2015) it is possible that high level of exposure
35
36 may be a preventable risk factor for cognitive impairment
37
38 or dementia (Heffernan and O'Neill 2013). A cross-sectional
39
40 research including 150 samples conducted in the North East
41
42 of England revealed that participants who had no history
43
44 of smoking and averagely exposed to SHS for around 6 years,
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46 showed significantly reduced performance in processing
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4 speed (i.e. how quickly one can process information and
5
6 perform tasks) and executive function(i.e. the ability to
7
8 organize memory, cognitive flexibility, and problem-
9
10 solving ability) as compared with non-exposed
11
12 people(Heffernan and O'Neill 2013). Such an inversed
13
14 relationship between environment tobacco smoke exposure and
15
16 visuospatial reasoning skills were also reported among
17
18 children and adolescents(Yolton, Dietrich et al. 2005).
19
20 Besides, a longitudinal aging study concerning 4809
21
22 samples(aged 50 years or older) had found that participants
23
24 were about 30 percent more likely to develop dementia when
25
26 exposed to SHS over a period of six years, compared with
27
28 those who never having been exposed; while this association
29
30 did not reach statistical significance after adjusting for
31
32 age, sex, and education ($P>0.05$)(Llewellyn, Lang et al.
33
34 2009).

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45 Few studies, however, have investigated the
46
47 relationship between household SHS exposure and different
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49 domains of cognitive function among elders. Previous
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51 studies of active smoking and cognitive impairment among
52
53 the Chinese population suggested that older current
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55 smokers(aged 63 years old on average)(Yolton, Dietrich et
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4 al. 2005) or those being exposed to SHS (aged between 55-64
5
6 years old) (Pan, Luo et al. 2018) were more likely to develop
7
8 cognitive impairment compared with never-smokers.
9
10 Nevertheless, both of them used only a 2-wave longitudinal
11
12 data and did not control for baseline cognition score.
13
14 Therefore, the primary aim of this study was to investigate
15
16 the relationship between secondhand smoking and cognitive
17
18 function among older non-smoking Chinese women, using a 3-
19
20 wave longitudinal national representative data. Through the
21
22 classification of respondents by different years of
23
24 secondhand smoke exposure in a 4-year panel, we identified
25
26 whether certain high SHS exposure groups were at higher
27
28 risk of cognitive decline than others after controlling for
29
30 demographic and socioeconomic factors. Besides, we aimed
31
32 to examine the association between secondhand smoke
33
34 exposure and cognitive subdomains. This is especially
35
36 important given the escalating aging trend and increasing
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38 prevalence of SHS exposure in China.
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56 **Methods**

57 **Data**

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4 We used data from 3 waves of the China Health and
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6 Retirement Longitudinal Study (CHARLS, 2011-2013-2015),
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8 which involved participants with a nationally
9
10 representative survey of adults aged 45 years or older, as
11
12 well as their spouses when possible. The CHARLS includes
13
14 assessments of social, economic, and health circumstances
15
16 of community-residents. The national baseline survey was
17
18 conducted between June 2011 and March 2012 and included
19
20 17,708 respondents from 10,257 households. CHARLS
21
22 respondents were followed every 2 years, using a face-to-
23
24 face computer-assisted personal interview (CAPI) (Zhao, Hu
25
26 et al. 2012). At baseline there was 3381 married women who
27
28 never smoked cigarettes and lived with spouses who had
29
30 either smoked cigarettes in the past or smoked at the time
31
32 of interview. Besides, all the data for each variable have
33
34 been collected for those respondents. Our final sample was
35
36 composed of 6875 respondents, among them 2802 were
37
38 interviewed again during the second wave of data collection
39
40 in 2013, and 2247 were interviewed again during the third
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42 wave in 2015. The similar sample selection process was
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44 conducted for participants in the second wave in 2013 as
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46 baseline, and final sample was consisted of 1799 women who
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4 were investigated again in 2015 as participants.
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8 **Measures**

10 ***Secondhand Smoke***

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12 Based on standardized CHARLS questionnaire, the exposure
13 to SHS among Chinese women was assessed through several
14 surveys, asking the participants about their current
15 marital status, the exact year they got married, and the
16 years the husband in each household has begun or ceased
17 smoking at home.
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28 The smoking status section contained four questions:
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30 "Have you ever chewed tobacco, smoked a pipe, smoked self-
31 rolled cigarettes, or smoked cigarettes/cigars?", "Do you
32 still have the habit or have you totally quit?", "At what
33 age did you totally quit smoking?" and "At what age did you
34 start to smoke on a regular basis?". If the answer to the
35 first question was "yes", they were defined as "current
36 smokers". Our analysis of SHS exposure focused only on
37 nonsmokers excluding the "current smokers", because of the
38 difficulty to differentiate the negative effects of active
39 smoking on health condition from that of SHS exposure. The
40 length of SHS exposure was calculated and expressed as the
41 total number of years that never-smoking women spent living
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4 with their spouses who smoked cigarettes at home. Based on
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6 the constructed SHS exposure variable, the participants
7
8 were classified into four different groups: Never or being
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10 exposed to secondhand smoke for less than 25 years, more
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12 than 25 years and less than 30 years, more than 30 years
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14 and less than 40 years and over 40 years.
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19 ***Cognitive function***

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22 Cognitive functions were measured from Telephone
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24 Interview of Cognition Status form (self-rated memory,
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26 today's date, day of the week, and current season); recall
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28 and delayed recall test of memory of 10 words; test of
29
30 serial subtractions of 7 from 100; ability to reproduce a
31
32 picture of two overlapped pentagons in CHARLS
33
34 questionnaires (Zhao, 2012. Cognitive subdomains including
35
36 visuospatial ability, orientation and attention, and
37
38 episodic memory (Ge, Wei et al. 2018) could be assessed by
39
40 these various sections of questionnaire. The Telephone
41
42 Interview of Cognitive Status (TICS) is a 10-item screening
43
44 test for the assessment of cognitive function in patients
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46 with Alzheimer's disease who are unwilling or unable to be
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48 examined in person. To assess orientation and attention
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50 function, the number of correct answers to above questions
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4 was scored and summed up (range 0 to 10). Figure drawing
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6 was used to measure a person's ability to identify visual
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8 and spatial relationships among objects. Participants who
9
10 successfully completed the task received a score of 1, and
11
12 those who failed received 0 (Ge, Wei et al. 2018).
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17 In addition, the word recall test was consisted of 2
18
19 components, immediate recall and delayed recall, and
20
21 evaluated episodic memory. Participants were required to
22
23 immediately repeat 10 Chinese nouns just read to them, and
24
25 after 20 questions concerning CES-D (approximately 4 to 10
26
27 minutes), they were again asked to recall as many of the
28
29 original words as possible. The item was coded as 1 if
30
31 recalled by the respondent, and as 0 if not. Scores for
32
33 immediate and delayed recall both varied from 0 to 10. An
34
35 evaluated episodic memory score was calculated using the
36
37 mean of scores in immediate and delayed word recall (range
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39 0 to 10) (Li, Cacchione et al. 2017).
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48 The overall cognition scores were the sum of the three
49
50 different domains (range 0 to 21).
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52 53 **Control variables**

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55 Given that cognitive function may vary across
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57 demographic and socioeconomic status, we thus included age,
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4 urban/rural residence, education, annual household
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6 expenditures, chronic diseases and depressive symptoms as
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8 control variables. Education was categorized into 3 groups:
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10 "illiterate", "primary education" and "secondary education
11
12 or above". Arterial hypertension and diabetes mellitus are
13
14 separately strong independent risk factors for the
15
16 development of cognitive impairment and dementia(Tadic,
17
18 Cuspidi et al. 2016) (Moheet, Mangia et al. 2015). Thus,
19
20 the baseline condition of hypertension and diabetes were
21
22 included, in addition to whether the participants were
23
24 being treated. The measure of depressive symptoms was based
25
26 on the 10-item version of the Center for Epidemiologic
27
28 Studies Depression Scale(CES-D) short form, and each of the
29
30 4-option response to item was scored ranging from 0 to 3.
31
32 The total score is the sum of points for all 10 items, and
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34 a score of 10 or higher suggests the presence of depressive
35
36 symptoms(Cheng, Chen et al. 2016).
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51 **Analysis**

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53 All analyses were conducted with STATA, version 14.0
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55 (Stata, College Station, TX, USA).We used lagged dependent-
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57 variable regression models with ordinary least squares
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4 estimation. In the LDV method, covariation both between and
5
6 within waves is used to estimate the coefficients, yielding
7
8 more stable estimates and lower standard errors than those
9
10 found in other methods, such as the change score (CS)
11
12 methods (Johnson 2005). After pooling the three sets of
13
14 panel data into one through using the "year" dummy variable
15
16 to differentiate between change in 2 years or in 4 years,
17
18 we have 6875 respondents who have complete data on all
19
20 variables. The overall cognitive scores, episodic memory
21
22 scores, visuospatial ability scores and orientation and
23
24 attention scores were 4 separate outcome variables. The
25
26 different groups of SHS exposure years were the predictor
27
28 variable, and other independent variables included all
29
30 demographic and socioeconomic characteristics. Prior to
31
32 fitting the regression models, descriptive analyses were
33
34 conducted to estimate the mean and standard deviations for
35
36 continuous data and frequencies and percentages for
37
38 categorical data.
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51 **Results**

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54 Table 1 provides a descriptive summary of all the
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56 variables for participants from each panel of three
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58 different waves: 2011-2013, 2011-2015 and 2013-2015. High
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4 prevalence of SHS exposure between 30 to 40 years were seen
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6 in different panels, accounting for 32.51%, 35.18% and
7
8 42.69% respectively.
9

10
11 The participants were over 45 years old, with the
12
13 average age of 56, 56 and 58 years old, respectively in
14
15 those waves . Participants were more likely to live in
16
17 rural area, have lower education background and do not have
18
19 hypertension or diabetes symptoms at baseline. In addition,
20
21 our results indicated that the average baseline cognition
22
23 scores were higher than wave-2 and wave-3 cognition scores.
24
25 The average scores of CES-D indicated high prevalence of
26
27 depression among Chinese middle-aged and old-aged women in
28
29 those years. Other socio-demographic characteristics of the
30
31 respondents are shown in Table 1
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40 Results from the regression models for the
41
42 relationship between SHS exposure and each domain of
43
44 cognitive function and overall cognition scores are
45
46 reported in Table 2 and Table 3. Scores of episodic
47
48 memory, orientation and attention and visuospatial among
49
50 respondents at baseline were strong predictors of their
51
52 corresponding cognitive function measures 2 or 4 years
53
54 later. Based on the analysis controlling age, annual
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4 household expenditure, education, baseline cognitive
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6 function and other chronic health status, we found that
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9 only being exposed to SHS for more than 40 years
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11 significantly resulted in a decline in visuospatial
12
13 abilities, episodic memory and overall cognition scores
14
15 for all respondents. Compared with respondents who were
16
17 not exposed to SHS or being exposed to it for less than
18
19 25 years, those who have exposed to SHS for more than 40
20
21 years suffered a 0.04-point decline in visuospatial
22
23 abilities (95%CI, -0.08--0.01 P <0.1), a 0.16-point decline in
24
25 episodic memory (95%CI, -0.31--0.01 P <0.05), and a 0.33-point
26
27 decline in overall cognition functions (95%CI, -0.66--0.01 P
28
29 <0.01). In addition, age was also a strong indicator. Each
30
31 one-year older resulted in a 0.01-point, 0.01-point,
32
33 0.03-point, 0.05-point decrease in visuospatial (95%CI, -
34
35 0.01--0.00 P <0.01), orientation (95%CI, -0.03--0.01 P <0.01),
36
37 memory (95%CI, -0.31--0.01 P <0.05) and overall cognition
38
39 scores (95%CI, -0.66--0.01 P <0.01), respectively. High
40
41 education level was associated with better cognitive
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43 performance, especially in orientation and attention.
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45 What's more, a one-point increase in CESD scores decrease
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47 0.02-point decrease in scores of orientation and
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4 attention(95%CI, -0.03--0.00 P <0.05), showing that
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6 respondents with depressive symptoms were more likely to
7
8 suffer from cognitive decline in specific functions.
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10

11 **Discussion**

12
13
14 Results from this longitudinal study with a large,
15
16 representative sample of middle-aged and older women in
17
18 China indicated that exposure to secondhand smoke for over
19
20 40 years was associated with significantly poorer
21
22 performance of global cognition and cognitive subdomains.
23
24 It is the first examination of cognitive subdomains in
25
26 relation to household SHS exposure using a 4-year
27
28 longitudinal data in China. The inferior performance of
29
30 passive smokers on measures of visuospatial abilities,
31
32 episodic memory and orientation and attention abilities are
33
34 creative as these domains were not specifically evaluated
35
36 in earlier studies with middle-aged and older samples who
37
38 never smoke(Durazzo, Meyerhoff et al. 2012).Previous study
39
40 only suggested that secondhand smoke was associated with
41
42 poorer cognitive performance specifically in children,
43
44 adolescents and adults(Yolton, Dietrich et al. 2005).
45
46 Besides, we found that having a high educational level,
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48 living in urban area and having better baseline cognitive
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4 function would improve their cognitive performance.
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6 Compared with those without diabetes, participants with
7
8 diabetes in baseline were found to have a 0.172-point
9
10 decline in episodic memory scores, whereas the exact type
11
12 of diabetes could not be examined in our study. An early
13
14 finding showed that people with both type 1 and type 2
15
16 diabetes had mild to moderate reductions in cognitive
17
18 function compared to non-diabetic controls as measured by
19
20 neuropsychological testing, while type 2 diabetes (T2DM),
21
22 but not type 1 diabetes, has been associated with 50%
23
24 increased risk of dementia (Moheet, Mangia et al. 2015).
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32 Our results showed that compared with women who have
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34 never been exposed to SHS or being exposed for less than
35
36 20 years, those who was exposed to SHS for more than 40
37
38 years have experienced, on average, 0.04-point, 0.16-point
39
40 and 0.33-point decline in scores of visuospatial function,
41
42 episodic memory and overall cognitive scores, respectively.
43
44 Compared with prior research (Pan, Luo et al. 2018), the
45
46 coefficients were significant. Besides, each one-year
47
48 increase in age resulted in a 0.01-point, 0.02-point, 0.04-
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50 point, 0.06-point decrease in visuospatial, orientation,
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52 memory and overall cognition scores, respectively.
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4 Secondhand smoke seems to be a stronger indicator of
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6 cognitive decline than aging. Study had reported that
7
8 attention referred to the ability to concentrate and focus
9
10 on specific stimuli slightly declined in later life (Lezak,
11
12 M; Howieson, D, 2012), and orientation was one's ability
13
14 to identify exact date, month, day and season of the year.
15
16 Our results did not signify the relationship between SHS
17
18 and orientation and attention ability may due to the
19
20 relatively small size of sample and short period of cohort
21
22 study after controlling for all demographic and
23
24 socioeconomic confounders. Visuospatial abilities involve
25
26 the ability to understand space in two and three dimensions.
27
28 A nationally representative data concerning 5683 children
29
30 and adolescents who were 6-16 years in America showed that
31
32 years of SHS exposure was significantly associated with
33
34 lower scores for reading, math, and visuospatial skills,
35
36 after adjusting for covariates (Yolton, Dietrich et al.
37
38 2005). In our study, an inversed relationship between SHS
39
40 exposure and visuospatial abilities among middle-aged and
41
42 older adults was also presented, showing a 0.04-point
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44 decline in their visuospatial scores. As one of the most
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46 common cognitive complaints among elders, episodic memory
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4 refers to personally experienced events which could be
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6 measured by stories, word lists or figures. Previous study
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8 proved that the onset of memory decline may vary among
9
10 different memory types, with episodic memory lasting
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12 lifelong (Rönnlund, M; Nyberg, L.2005). Our study could not
13
14 prove the onset age of memory decline without doing
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16 regression among different age groups, while the memory
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18 decline caused by SHS could be presented by the significant
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20 coefficient.
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27 The inconsistent conclusions between our studies and
28
29 prior ones may probably due to the relatively simplified
30
31 version of cognition test procedure in CHARLS
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33 questionnaires compared with the MoCA(Li, Jia et al. 2018)
34
35 and MMSE(Trzepacz, Hochstetler et al. 2015). Some studies
36
37 also used clinical or magnetic resonance imaging (MRI)
38
39 evidence of neurologic damage to detect cognitive
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41 impairment (Kalb R,etal2018). Best adapted to a screening test,
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43 the MoCA exhibited excellent sensitivity in identifying MCI
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45 and AD(Alzheimer's disease) by 90% and 100%, respectively
46
47 (Ziad S. Nasreddine 2005).
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56 The most popular hypothesis about the mechanisms
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58 underlying the links between SHS exposure and poorer
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4 cognitive performance lies in the notion that the carbon
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6 monoxide (CO) in tobacco smoke may interfere with the
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8 oxygen being delivered to the brain via the blood system,
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10 which could be tested by measuring levels of CO in the
11
12 blood of never smokers who have been exposed to SHS and
13
14 comparing these with never smokers with no history of such
15
16 exposure. However, the reasons behind different effect on
17
18 various domains of brain function are far from clear. One
19
20 possible explanation derives from an animal research. It
21
22 may lead to reduced neuronal mass in specific regions of
23
24 the brain associated with learning and memory after
25
26 exposing animals to varying degrees of toxic mixtures of
27
28 chemicals found in tobacco smoke. Since the hippocampal
29
30 region of the brain is known to be involved in the
31
32 mediation of memory(Staples and Mandyam 2016) and learning,
33
34 further research should be conducted in other regions
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36 dominating visuospatial and orientation ability. Another
37
38 possible mechanism is that prolonged exposure to SHS may
39
40 be a significant risk factor for cardiovascular disease
41
42 (Yankelevitz, Henschke et al. 2013), which may therefore
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44 lead to a range of health and cognitive problems in later
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46 life. A longitudinal design could elucidate this
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4 association by observing long-term exposure to SHS and a
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6 potential build-up of CVD as well as how these correlates
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9 with performance upon a range of cognitive measures.

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11 Several limitations need to be considered when
12
13 interpreting this study and designing future studies.
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15 Firstly, the exposure to secondhand smoke was evaluated
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17 based on self-report measures. This might be subject to
18
19 recall bias and led to over-or-underestimation of
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21 exposure (Ling and Heffernan 2016). Therefore, further
22
23 studies could include more biological assays, for example,
24
25 cotinine residue levels or nicotine residue in saliva or
26
27 hair samples (Akhtar, Andresen et al. 2013). Previous
28
29 research using serum cotinine as a biomarker of exposure
30
31 to SHS found that higher levels of serum cotinine were
32
33 associated with significant reductions in performance in
34
35 reading, mathematics, and visual and spatial abilities in
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37 children and adolescents (Yolton, Dietrich et al. 2005).
38
39 However, no studies had used a combination of biomarker and
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41 self-report yet (Stirland, O'Shea et al. 2018). Cognitive
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43 impairment could also be detected by the effect of
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45 apolipoprotein $\epsilon 4$ (Apo $\epsilon 4$) polymorphism, which was a known
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47 risk factor for dementia. Secondly, it may be impossible
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4 to control for all potentially confounding variables. After
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6 adjusting for age, household expenditure, education, area,
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8 chronic health condition and depressive symptoms, some
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10 other demographic or socioeconomic confounders may be
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12 neglected. Nevertheless, this did not appear to affect the
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14 magnitude of the association between SHS exposure and
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16 cognition (Chen, Clifford et al. 2013). Besides, the analyses
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18 only contained household SHS exposure, which precludes the
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20 analyses of the influence of environment smoke inhale on
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22 smoking proclivity. Whether exposure to household SHS can
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24 hasten the onset of cognitive impairment for older Chinese
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26 women could be further proved by running regression models
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28 in different age groups.
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42 Research, Peking University for her thoughtful contributions to this study.
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44

45 **Conflict of Interest**

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48 The authors have no conflicts of interest to declare.
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50 **Author's Contribution**

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53 Anying Bai wrote and participated in all aspects of this research, including the field
54
55 investigation. Dr Yangmu Huang reviewed and supervised this research. Yinzi Jin
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57 participated in the statistical analysis of this work and reviewed the final article.
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Data sharing statement

CHARLS data is available to the public online : <http://charls.pku.edu.cn>

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Table 1. Characteristics of the Participants from 3 waves of CHARLS, 2011-2013-2015

Variable	2011-2013 (N=2802)		2011-2015 (N=2274)		2013-2015 (N=1799)	
	Count	Frequency	Count	Frequency	Count	Frequency
Area						
Urban	981	35.01%	730	32.10%	556	30.91%
Rural	1821	64.99%	1544	67.90%	1243	69.09%
Secondhand Smoke						
Less than 25 years	759	27.09%	531	23.35%	262	14.56%
More than 25 years and less than 30 years	634	22.63%	573	25.20%	385	21.40%
More than 30 years and less than 40 years	911	32.51%	800	35.18%	768	42.69%
More than 40 years	498	17.77%	370	16.27%	384	21.35%
Education						
Illiterate	1552	55.39%	1309	57.56%	1004	55.81%
Primary education	512	18.27%	414	18.21%	336	18.68%
Secondary or above	738	26.34%	551	24.23%	459	25.51%
Hypertension						
No hypertension	2124	75.80%	1720	75.64%	1365	75.88%
Hypertension with treatment	522	18.63%	1720	75.64%	358	19.90%
Hypertension without treatment	156	5.57%	130	5.72%	76	4.22%
Diabetes						
No Diabetes in baseline	2643	94.33%	2140	94.11%	1704	94.72%

Have Diabetes with treatment	143	5.10%	120	5.28%	86	4.78%
Have Diabetes without treatment	16	0.57%	14	0.62%	9	0.50%
	Count	Mean (SD)	Count	Mean (SD)	Count	Mean (SD)
Age	2802	55.84 (8.22)	2274	56.19 (7.75)	1799	57.90 (7.43)
Annual Household Expenditure, yuan ^a	2802	13786.99 (14197.29)	2274	13060.14 (13639.33)	1799	16632.84 (18568.24)
Visuospatial ability ^b	2802	0.51 (0.50)	2274	0.48 (0.50)	1799	0.49 (0.50)
Orientation and attention ^c	2802	5.87 (3.29)	2274	5.84 (3.19)	1799	5.97 (3.14)
Memory Scores ^d	2802	3.33 (1.96)	2274	3.04 (1.93)	1799	3.15 (1.91)
Baseline Visuospatial ability	2802	0.57 (0.50)	2274	0.55 (0.50)	1799	0.54 (0.50)
Baseline Orientation and attention	2802	6.39 (2.92)	2274	6.25 (2.90)	1799	6.16 (3.00)
Baseline Memory Scores	2802	3.27 (1.98)	2274	3.23 (1.92)	1799	3.50 (1.78)
Baseline CES-D Score ^e	2802	12.09 (5.38)	2274	12.13 (5.45)	1799	10.90 (5.14)

Abbreviation: SHS, secondhand smoke.

a 1 US dollar = 6.3 yuan.

b The score range for visuospatial ability was 0-1.

c The score range for orientation and attention was 0-10. Higher scores indicate better mental status.

d The score range for episodic memory was 0-10. Higher scores indicate better memory function.

e A score of 10 or greater indicated the presence of depressive symptoms.

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Table 2. Multivariable linear regression analysis of the relationship between smoking exposure and Visuospatial function and Orientation and Attention among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Visuospatial Scores			Orientation and Attention		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.01 ^a	-0.01, -0.00	-6.73	-0.02 ^a	-0.03, -0.01	-4.34
Expenditure	0.00	0.00, 0.00	0.01	0.00 ^a	0.00, 0.00	0.77
Secondhand Smoke Exposure^d						
More than 25 years less than 30 years	-0.01	-0.04, 0.02	-0.72	0.05	-0.12, 0.21	0.56
More than 30 years less than 40 years	-0.02	-0.05, 0.02	-0.95	-0.03	-0.20, 0.13	-0.38
More than 40 years	-0.04 ^c	-0.08, 0.01	-1.67	-0.15	-0.38, 0.09	-1.24
Baseline Visuospatial Scores	0.23 ^a	0.21, 0.26	17.93			
Baseline Orientation Scores				0.55 ^a	0.53, 0.57	44.86

Urban ^e	0.06 ^a	0.04, 0.09	5.27	0.38 ^a	0.25, 0.51	5.72
Education^f						
Primary	0.23 ^a	0.20, 0.26	14.00	1.11 ^a	0.94, 1.27	12.91
Secondary or Above	0.29 ^a	0.26, 0.32	18.51	1.18 ^a	1.01, 1.36	13.44
Hypertension^g						
With Treatment	-0.03	-0.09, 0.02	-1.20	0.06	-0.24, 0.35	-0.38
Without Treatment	-0.02	-0.06, 0.03	-0.69	0.06	-0.11, 0.24	0.04
Missing Group	-0.05 ^c	-0.12, 0.01	-1.67	0.06	-0.19, 0.30	-0.01
Diabetes^h						
With Treatment	0.02	-0.03, 0.07	0.90	0.25 ^c	-0.03, 0.52	-1.77
Without Treatment	0.03	-0.04, 0.09	0.82	0.21	-0.06, 0.48	-0.23
Missing Group	0.07	-0.08, 0.21	0.88	0.50	-0.22, 1.23	0.67
Baseline CES-D Score						
	-0.00 ^c	-0.00, 0.00	-1.71	-0.02 ^b	-0.03, -0.00	-2.57
year = 2						
	-0.02	-0.04, 0.01	-1.58	0.09	-0.05, 0.22	1.29

Abbreviations: CI, confidence interval; SHS, secondhand smoke.

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- a. $p < 0.01$
- b. $p < 0.05$
- c. $p < 0.1$
- d. Referent: No SHS exposure or Less than 25 years.
- e. Expenditure is expressed as the natural log of the annual household expenditure
- f. Referent: Illiterate
- g. Referent: Without hypertension
- h. Referent: Without diabetes

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Table 3. Multivariable linear regression analysis of the relationship between smoking exposure and Episodic memory and Overall cognitive function among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Episodic Memory			Overall Cognition Scores		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.04 ^a	-0.05, -0.03	-11.37	-0.06 ^a	-0.07, -0.04	-7.87
Expenditure	0.00	0.00, 0.00	1.30	0.00 ^a	0.00, 0.00	0.32
Secondhand Smoke Exposure^d						
More than 25 years less than 30 years	-0.04	-0.16, 0.08	-0.67	-0.01	-0.25, 0.25	-0.01
More than 30 years less than 40 years	0.02	-0.09, 0.13	0.36	-0.05	-0.29, 0.19	-0.41
More than 40 years	-0.16 ^b	-0.31, -0.01	-2.06	-0.33 ^a	-0.66, 0.01	-1.93
Baseline Memory Scores	0.30 ^a	0.28, 0.32	25.22			

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5	Baseline Cognition Scores				0.55 ^a	0.46, 0.83	44.95
6							
7	Urban^e	0.25 ^a	0.16, 0.34	5.60	0.65 ^a	0.46, 0.83	6.68
8							
9							
10	Education^f						
11	Primary	0.70 ^a	0.58, 0.80	12.42	1.77 ^a	1.53, 2.02	14.28
12							
13							
14	Secondary or Above	0.97 ^a	0.86, 1.08	17.29	2.00 ^a	1.74, 2.26	15.24
15							
16							
17	Hypertension^g						
18	With Treatment	0.04	-0.16, 0.23	0.35	0.13	-0.29, 0.56	0.62
19							
20	Without Treatment	0.06	-0.06, 0.17	0.95	0.12	-0.14, 0.38	0.93
21							
22							
23	Missing Group	0.07	-0.12, 0.25	0.70	0.10	-0.27, 0.47	0.52
24							
25							
26	Diabetes^h						
27	With Treatment	-0.20 ^b	-0.38, 0.02	-2.20	-0.04	-0.43, 0.36	0.62
28							
29	Without Treatment	-0.07	-0.25, 0.11	-0.77	0.08	-0.30, 0.47	0.43
30							
31							
32	Missing Group	0.32	-0.16, 0.80	1.30	0.87	-0.11, 1.84	1.75
33							
34							
35	Baseline CES-D Score	-0.01 ^b	-0.01, 0.00	-1.59	-0.01	-0.03, 0.00	-2.57
36							
37	year = 2	-0.24	-0.33, -0.15	-5.21	-0.17	-0.37, 0.03	-1.70
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Constant	0.63	0.53, 0.74	11.54	6.48 ^a	5.59, 7.37	14.28
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Abbreviations: CI, confidence interval; SHS, secondhand smoke.

a. $p < 0.01$

b. $p < 0.05$

c. $p < 0.1$

d. Referent: No SHS exposure or Less than 25 years.

e. Expenditure is expressed as the natural log of the annual household expenditure

f. Referent: Illiterate

g. Referent: Without hypertension

h. Referent: Without diabetes

Reporting checklist for qualitative study.

Based on the SRQR guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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	Reporting Item	Page Number
Title		
	#1 Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g. ethnography, grounded theory) or data collection methods (e.g. interview, focus group) is recommended	1
Abstract		
	#2 Summary of the key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results and conclusions	2
Introduction		
Problem formulation	#3 Description and significance of the problem / phenomenon studied: review of relevant theory and empirical work; problem statement	4
Purpose or research question	#4 Purpose of the study and specific objectives or questions	5

1 **Methods**

2			
3	Qualitative approach and	#5	Qualitative approach (e.g. ethnography, grounded theory, case
4	research paradigm		study, phenomenology, narrative research) and guiding theory
5			if appropriate; identifying the research paradigm (e.g.
6			postpositivist, constructivist / interpretivist) is also
7			recommended; rationale. The rationale should briefly discuss
8			the justification for choosing that theory, approach, method or
9			technique rather than other options available; the assumptions
10			and limitations implicit in those choices and how those
11			choices influence study conclusions and transferability. As
12			appropriate the rationale for several items might be discussed
13			together.
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20	Researcher characteristics	#6	Researchers' characteristics that may influence the research,
21	and reflexivity		including personal attributes, qualifications / experience,
22			relationship with participants, assumptions and / or
23			presuppositions; potential or actual interaction between
24			researchers' characteristics and the research questions,
25			approach, methods, results and / or transferability
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30	Context	#7	Setting / site and salient contextual factors; rationale
31			
32			
33	Sampling strategy	#8	How and why research participants, documents, or events
34			were selected; criteria for deciding when no further sampling
35			was necessary (e.g. sampling saturation); rationale
36			
37			
38	Ethical issues pertaining to	#9	Documentation of approval by an appropriate ethics review
39	human subjects		board and participant consent, or explanation for lack thereof;
40			other confidentiality and data security issues
41			
42			
43	Data collection methods	#10	Types of data collected; details of data collection procedures
44			including (as appropriate) start and stop dates of data
45			collection and analysis, iterative process, triangulation of
46			sources / methods, and modification of procedures in response
47			to evolving study findings; rationale
48			
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50			
51	Data collection instruments	#11	Description of instruments (e.g. interview guides,
52	and technologies		questionnaires) and devices (e.g. audio recorders) used for
53			data collection; if / how the instruments(s) changed over the
54			course of the study
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1	Units of study	#12	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	7
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6	Data processing	#13	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymisation / deidentification of excerpts	10
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13	Data analysis	#14	Process by which inferences, themes, etc. were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale	11
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18	Techniques to enhance trustworthiness	#15	Techniques to enhance trustworthiness and credibility of data analysis (e.g. member checking, audit trail, triangulation); rationale	10
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24	Results/findings			
25				
26	Syntheses and interpretation	#16	Main findings (e.g. interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	11
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31	Links to empirical data	#17	Evidence (e.g. quotes, field notes, text excerpts, photographs) to substantiate analytic findings	11
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35	Discussion			
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38	Intergration with prior work, implications, transferability and contribution(s) to the field	#18	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application / generalizability; identification of unique contributions(s) to scholarship in a discipline or field	13
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46	Limitations	#19	Trustworthiness and limitations of findings	15
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48	Other			
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51	Conflicts of interest	#20	Potential sources of influence of perceived influence on study conduct and conclusions; how these were managed	17
52				
53				
54	Funding	#21	Sources of funding and other support; role of funders in data collection, interpretation and reporting	17
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3 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Exposure to Secondhand Smoke and Cognitive Function Among Middle-aged and Older Women in China: Findings of 3-waves of the China Health and Retirement Longitudinal Study

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Title

Exposure to Secondhand Smoke and Cognitive Function Among
Middle-aged and Older Women in China: Findings of 3-waves
of the China Health and Retirement Longitudinal Study

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Abstract

Objectives: To examine the association between secondhand smoke and women's global cognitive function and cognitive subdomains.

Design: Cohort study

Participants: Data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS, 2011-2013-2015), and pooled analysis was applied to wave 1 and wave 2 (2011-2013), wave 2 and wave 3 (2013-2015) and wave 1 and wave 3 (2011-2015). Data from a total of 6875 Chinese women with normal cognitive function in baseline were selected for analysis, including 2981 who were interviewed in 2011, 2471 in 2013, and 1894 in 2015.

Main outcome measures and methods: Secondhand smoke was classified based on length of exposed years (<25years, ≥ 25 to <30 years, ≥30 to <40 years, ≥40 years). Global cognitive function, visuospatial ability, orientation and attention, and episodic memory function were used as measures of cognitive function. We pooled the three waves of data by using dummy variable to differentiate between

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4 2-year and 4-year. Lagged dependent variable models were
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6 used to examine independent associations between
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8 secondhand smoke and cognitive function. Demographic
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10 factors, socioeconomic factors, baseline cognitive
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12 functioning and health conditions were controlled in our
13
14 models.
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19 **Results:** Secondhand smoke was found to be inversely and
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21 significantly associated with cognitive function.
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23 Compared with those had not been exposed to household
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25 secondhand smoke, women who had lived with a smoking
26
27 husband had significantly faster cognition decline,
28
29 especially in global cognitive function ($\beta=-0.33$, 95%CI, -0.66--
30
31 0.01, $P<0.01$), visuospatial ability ($\beta=-0.04$, 95%CI, -0.08--0.01 P
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33 < 0.05) and episodic memory function ($\beta=-0.16$, 95%CI, -0.31--
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35 -0.01 $P = 0.031$).
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43 **Conclusions:** Secondhand smoke within household is a risk
44
45 factor for cognitive decline among Chinese non-smoking
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47 women. Being exposed to secondhand smoke for more than 40
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49 years was associated with greater decline in global
50
51 cognitive function, visuospatial ability and episodic
52
53 memory function, but not in orientation and attention
54
55 function among elder Chinese women.
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Key words: aging; passive smoking; panel analysis; visuospatial ability; memory

Strengths and limitations of this study:

- This is the first study to investigate on the association between secondhand smoke exposure and women's different domains of cognitive functions in China using a 4-year longitudinal national representative data.
- This study addressed the issue of reverse causation in observational cohort studies by used lagged dependent variable models and adjust for baseline cognition scores
- The exposure to secondhand smoke was evaluated based on self-report measures.
- The analyses only contained household SHS exposure and excluding environmental exposure.

Word Count: 3214

Number of references:31

Number of data elements :1

Introduction

China's population has been ageing rapidly. By 2050, there will be 400 million Chinese citizens aged over 65 years old, and 150 million of whom will be older than 80

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4 years old^[1]. It will become increasingly important to
5
6 understand the cognitive changes that accompany aging^[2].
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8 Cognitive impairment, described as a decline in
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10 intellectual functions ^[3], ranges from mild forms of
11
12 forgetfulness to severe and debilitating dementia ^[4]. The
13
14 prevalence of cognitive impairment is rising, with national
15
16 figures estimating that around 9% of older persons in China
17
18 had cognitive impairment in 2011 ^[4].
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25 Numerous determinants such as environmental, individual,
26
27 and genetic factors could favor evolution toward cognitive
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29 impairment, and both age and late-life hypertension
30
31 increase the risk of dementia over time ^[5]. The mechanism
32
33 lies in age-related functional and structural changes in
34
35 cerebrovascular small and large blood vessels ^[6]. Besides
36
37 chronic diseases factors, depression has long been known
38
39 to affect memory and other neurocognitive domains, and be
40
41 associated with an increased risk of developing mild
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43 cognitive impairment (MCI) in cognitively normal elderly
44
45 people ^[7].
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53 Exposure to secondhand smoke (SHS), also known as
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55 "passive smoking," refers to a situation where a never-
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57 smoker inhales another person's smoke either by exposure
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4 to side stream smoke or mainstream smoke ^[8]. Current smoking
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6 prevalence in China decreased from 31.1% in 2002 to 28.1%
7
8 in 2010; however, the number of adults exposed to
9
10 secondhand smoke during this period still increased from
11
12 540 million to 556 million ^[2]. The negative health effects
13
14 of high levels of exposure to SHS may be close to those of
15
16 active smoking, including inferior performance on measures
17
18 of general intelligence, visuospatial learning and memory
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20 and fine motor dexterity ^[9]. Given the association between
21
22 exposure to SHS and risk factors for cognitive impairment
23
24 such as cardiovascular disease ^[10], hypertension ^[11], and
25
26 stroke ^[12], it is possible that high level of exposure may
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28 be a preventable risk factor for cognitive impairment or
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30 dementia ^[13].

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40 Several studies have shown that exposure of SHS and
41
42 cognitive impairment are interrelated ^[13-15]. However, much
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44 less is known about whether and to what extent SHS is
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46 associated with global and subdomains of cognitive function
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48 among elder women in China. Previous studies of active
49
50 smoking and cognitive impairment among the Chinese
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52 population suggested that older current smokers (aged 63
53
54 years old on average) ^[14] or those being exposed to SHS
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(aged between 55-64 years old) ^[16] were more likely to develop cognitive impairment compared with never-smokers. Nevertheless, both of them used only a 2-wave longitudinal data and did not control for baseline cognition. Therefore, the primary aim of this study was to investigate the relationship between secondhand smoke and cognitive function among older non-smoking Chinese women, using a 3-wave longitudinal national representative data. Through the classification of respondents by different years of secondhand smoke exposure in a 4-year panel, we identified whether certain high SHS exposure groups were at higher risk of cognitive decline than others after controlling for confounders. Besides, we aimed to examine the association between secondhand smoke exposure and cognitive subdomains. This is especially important given the escalating aging trend and increasing prevalence of SHS exposure in China.

Methods

Data

CHARLS had passed the ethical review before field investigation and we used data from 3 waves of the China Health and Retirement Longitudinal Study (CHARLS,2011-2013-2015), which was publicly available at <http://charls.pku.edu.cn>. CHARLS involved participants with a nationally

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4 representative survey of adults aged 45 years or older, as
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6 well as their spouses when possible, and included
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8 assessments of social, economic, and health circumstances
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10 of community-residents. The national baseline survey was
11
12 conducted between June 2011 and March 2012 and samples were
13
14 chosen through multistage probability sampling. After
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16 excluding empty or non-resident dwellings, final interviews
17
18 were conducted on 17,708 respondents from 10,257 households,
19
20 which completed at least one module of the survey beyond
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22 the cover screening for age eligibility. CHARLS respondents
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24 were followed every 2 years, using a face-to-face computer-
25
26 assisted personal interview (CAPI) ^[17]. At baseline there
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28 was 3381 married women who never smoked cigarettes and
29
30 lived with spouses who had either smoked cigarettes in the
31
32 past or smoked at the time of interview. Besides, all the
33
34 data for each variable have been collected for those
35
36 respondents. Our final sample was composed of 6875
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38 respondents, among them 2802 were interviewed again during
39
40 the second wave of data collection in 2013, and 2247 were
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42 interviewed again during the third wave in 2015. The
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44 similar sample selection process was conducted for
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46 participants in the second wave in 2013 as baseline, and
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4 final sample was consisted of 1799 women who were
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6 investigated again in 2015 as participants.
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10 **Measures**

11 ***Secondhand Smoke***

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15 Based on standardized CHARLS questionnaire, the exposure
16
17 to SHS among Chinese women was assessed through several
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19 surveys, asking the participants about their current
20
21 marital status, the exact year they got married, and the
22
23 year the husband in each household has begun or ceased
24
25 smoking at home.
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31 The smoking status section contained four questions:
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33 "Have you ever chewed tobacco, smoked a pipe, smoked self-
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35 rolled cigarettes, or smoked cigarettes/cigars?", "Do you
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37 still have the habit or have you totally quit?", "At what
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39 age did you totally quit smoking?" and "At what age did you
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41 start to smoke on a regular basis?". If the answer to the
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43 first question was "yes", they were defined as "current
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45 smokers". Our analysis of SHS exposure focused only on
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47 never smokers excluding the "current smokers", because of
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49 the difficulty to differentiate the negative effects of
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51 active smoking on health condition from that of SHS
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53 exposure. The length of SHS exposure was calculated and
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expressed as the total number of years that never-smoking women spent living with their spouses who smoked cigarettes at home. Based on the constructed SHS exposure variable, the participants were classified into four different groups: Never or being exposed to secondhand smoke for less than 25 years, more than 25 years and less than 30 years, more than 30 years and less than 40 years and over 40 years.

Cognitive function

The cognitive function of the respondents in CHARLS questionnaires was measured through a question-and-answer interview instrument, and the respondents would be followed every two years using a face-to-face, computer-aided personal interview (CAPI). Cognitive subdomains including visuospatial ability, orientation and attention, and episodic memory could be assessed by these various sections of questionnaire. Figure drawing was tested by asking the participants to reproduce a picture of two overlapped pentagons in CHARLS questionnaires^[17], and was used to measure a person's ability to identify visual and spatial relationships among objects. The Telephone Interview of Cognitive Status (TICS) was a screening test including serial subtractions of 7 from 100 (up to 5 times), date (month, day, and year and season), and the day of the week. To assess orientation and attention function, the number of correct answers to above questions in TICS was scored and

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4 summed up (range 0 to 10). Participants who successfully completed the task received
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6 a score of 1, and those who failed received 0^[18].
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9 In addition, the word recall test was consisted of 2
10 components, immediate recall and delayed recall, and
11 evaluated episodic memory. Participants were required to
12 immediately repeat 10 Chinese nouns just read to them, and
13 after 20 questions concerning Center for Epidemiologic
14 Studies Depression Scale (CES-D, approximately 4 to 10
15 minutes), they were again asked to recall as many of the
16 original words as possible. The item was coded as 1 if
17 recalled by the respondent, and as 0 if not. Scores for
18 immediate and delayed recall both varied from 0 to 10. An
19 evaluated episodic memory score was calculated using the
20 mean of scores in immediate and delayed word recall (range
21 0 to 10)^[19].
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43 The overall cognition scores were the sum of the three
44 different domains (range 0 to 21).
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48 ***Control variables***

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50 Given that cognitive function may vary across
51 demographic and socioeconomic status, we thus included age,
52 urban/rural residence, education, annual household
53 expenditures, chronic diseases and depressive symptoms as
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control variables. Education was categorized into 3 groups: "illiterate", "primary education" and "secondary education or above". Arterial hypertension and diabetes mellitus are separately strong independent risk factors for the development of cognitive impairment and dementia^[6] [20]. Thus, the baseline chronic disease of hypertension and diabetes were classified as three types based on self-reported conditions on whether the participants were being treated: having hypertension/diabetes with treatment, having hypertension/diabetes without treatment and not having hypertension/diabetes. The measure of depressive symptoms was based on the 10-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) short form, and each of the 4-option response to item was scored ranging from 0 to 3. The total score is the sum of points for all 10 items, and a score of 10 or higher suggests the presence of depressive symptoms .

Patient and Public Involvement

No patient involved.

Analysis

All analyses were conducted with STATA, version 14.0 (Stata, College Station, TX, USA). We used lagged dependent-

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4 variable regression models with ordinary least squares
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6 estimation. LDV models were superior for analyzing the
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8 effects of predictor variables on an outcome with 2-wave
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10 panel data while controlling for the influence of time-
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12 invariant variables ^[16]. It adjusted for baseline cognitive
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14 conditions for all participants, therefore provided more
15
16 robust estimates of the effects of independent variables.
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18 After pooling the three sets of panel data into one through
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20 using the "year" dummy variable to differentiate between
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22 change in 2 years or in 4 years, we have 6875 respondents
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24 who have complete data on all variables. The overall
25
26 cognitive scores, episodic memory scores, visuospatial
27
28 ability scores and orientation and attention scores were 4
29
30 separate outcome variables. The different groups of SHS
31
32 exposure years were the predictor variable, and other
33
34 independent variables included all demographic and
35
36 socioeconomic characteristics. Prior to fitting the
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38 regression models, descriptive analyses were conducted to
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40 estimate the mean and standard deviations for continuous
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42 data and frequencies and percentages for categorical data.
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57 **Results**

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59 Table 1 provides a descriptive summary of all the
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4 variables for participants from each panel of three
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6 different waves: 2011-2013, 2011-2015 and 2013-2015. High
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8 prevalence of SHS exposure between 30 to 40 years were seen
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10 in different panels, accounting for 32.51%, 35.18% and
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12 42.69% respectively.
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15
16 The participants were over 45 years old, with the
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18 average age of 56, 56 and 58 years old, respectively in
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20 those waves. Participants were more likely to live in rural
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22 area, have lower education background and do not have
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24 hypertension or diabetes diagnose at baseline. In addition,
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26 our results indicated that the average baseline cognition
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28 scores were higher than cognition scores after 2 or 4 years.
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30 The average scores of Center for Epidemiologic Studies
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32 Depression Scale (CES-D) indicated that the prevalence of
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34 depression among Chinese middle-aged and old-aged women
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36 were high in those years. Other socio-demographic
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38 characteristics of the respondents are shown in Table 1
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48 Results from the regression models for the
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50 relationship between SHS exposure and each domain of
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52 cognitive function and overall cognition scores are
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54 reported in Table 2 and Table 3. Scores of episodic
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56 memory, orientation and attention and visuospatial among
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4 respondents at baseline were strong predictors of their
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6 corresponding cognitive function measures after 2 or 4
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8 years. Based on the analysis adjusted for age, annual
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10 household expenditure, education, baseline cognitive
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12 function and other chronic health status, we found that
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14 only being exposed to SHS for more than 40 years
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16 significantly resulted in a decline in visuospatial
17
18 abilities, episodic memory and overall cognition scores
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20 for all respondents. Compared with respondents who were
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22 not exposed to SHS or exposed to it for less than 25
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24 years, those who have been exposed to SHS for more than
25
26 40 years was associated with 0.04-point decline in
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28 visuospatial abilities (95%CI, -0.08--0.01 P <0.1), 0.16-
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30 point decline in episodic memory (95%CI, -0.31--0.01 P
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32 <0.05), and 0.33-point decline in overall cognition
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34 function (95%CI, -0.66--0.01 P <0.01). In addition, age was
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36 also negatively associated with cognitive function. Each
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38 one-year older resulted in 0.01-point, 0.01-point, 0.03-
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40 point, and 0.05-point decrease in visuospatial (95%CI, -
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42 0.01--0.00 P <0.01), orientation (95%CI, -0.03---0.01 P <0.01),
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44 memory (95%CI, -0.31---0.01 P <0.05) and overall cognition
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46 scores (95%CI, -0.66---0.01 P <0.01), respectively. High
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4 education level was associated with better cognitive
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6 performance, especially in orientation and attention.
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9 What's more, one-point increase in CESD scores was
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11 associated with 0.02-point decrease in scores of
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13 orientation and attention (95%CI, -0.03--0.00 P <0.05),
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15 showing that respondents with depressive symptoms were
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17 more likely to demonstrate cognitive decline in specific
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19 functions.
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25 **Discussion**

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27 Results from this longitudinal study with a large,
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29 representative sample of middle-aged and older women in
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31 China indicated that exposure to secondhand smoke for over
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33 40 years was significantly associated with poorer
34
35 performance of global cognition and cognitive subdomains.
36
37 It is the first examination of cognitive subdomains in
38
39 relation to household SHS exposure using a 4-year
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41 longitudinal data in China. The inferior performance of
42
43 secondhand smoke on visuospatial abilities, episodic memory
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45 and orientation and attention abilities are novel as these
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47 domains were not specifically evaluated in earlier studies
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49 among middle-aged and older women who never smoke
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58 [9]. Previous study only suggested that secondhand smoke was
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4 associated with poorer cognitive performance, specifically
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6 in children, adolescents and adults ^[14]. Besides, we found
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8 that having a high educational level, living in urban area
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10 and having better baseline cognitive function would improve
11
12 their cognitive performance. Compared with those without
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14 diabetes, participants with diabetes in baseline were found
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16 to have a 0.172-point decline in episodic memory scores,
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18 which is similar to the previous findings ^[20].
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25 Our results showed that compared with women who have
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27 never been exposed to SHS or have been exposed for less
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29 than 20 years, those who have been exposed to SHS for more
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31 than 40 years experienced 0.04-point, 0.16-point and 0.33-
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33 point of decline in scores of visuospatial function,
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35 episodic memory and overall cognitive scores, respectively.
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38 Our results were quite similar in magnitude to prior
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40 research on the relationship between SHS and cognitive
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42 function ^[16]. A cross-sectional research including 150
43
44 samples conducted in the North East of England revealed
45
46 that participants who had no history of smoking and being
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48 averagely exposed to SHS for around 6 years showed
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50 significantly reduced performance in processing speed (i.e.
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52 how quickly one can process information and perform tasks)
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4 and executive function (i.e. the ability to organize memory,
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6 cognitive flexibility, and problem-solving ability) as
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9 compared with non-exposed people^[13]. Another longitudinal
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11 aging study concerning 4809 samples (aged 50 years or older)
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13
14 found that never smokers exposed to the highest levels of
15
16 SHS (salivary cotinine concentrations 0.8-13.5 ng/ml) were
17
18 more likely to be cognitively impaired (odds ratio 1.70,
19
20 1.03 to 2.80) than those exposed to little or no SHS^[15].
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24 Besides, each one-year increase in age resulted in a
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26 0.01-point, 0.02-point, 0.04-point, 0.06-point decrease in
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28 visuospatial, orientation, memory and overall cognition
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30 scores, respectively. Secondhand smoke seems to be more
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32 strongly associated with cognitive decline than aging.
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35 Study had reported that attention referred to the ability
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37 to concentrate and focus on specific stimuli slightly
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39 declined in later life ^[21], and orientation was one's
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41 ability to identify exact date, month, day and season of
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43 the year. Our results did not observe the relationship
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45 between SHS and orientation and attention ability, which
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47 may due to the relatively small size of sample and short
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49 period of cohort study after controlling for all
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51 demographic and socioeconomic confounders. Visuospatial
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4 abilities involve the ability to understand space in two
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6 and three dimensions. In our study, an inversed relationship
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9 between SHS exposure and visuospatial abilities among
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11 middle-aged and older adults was presented, showing a 0.04-
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13 point decline in their visuospatial scores. Such an
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15 inversed relationship between SHS exposure and visuospatial
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17 reasoning skills were also reported among 5683 children
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19 aged 6-16 years in America, showing that years of SHS
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21 exposure was significantly associated with lower scores for
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23 reading, math, and visuospatial skills, after adjusting for
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25 covariates ^[14]. As one of the most common cognitive
26
27 complaints among elders, episodic memory refers to
28
29 personally experienced events which could be measured by
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31 stories, word lists or figures. Previous study proved that
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33 the onset of memory decline may vary among different memory
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35 types, with episodic memory lasting lifelong ^[22]. Our study
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37 could not prove the onset age of memory decline without
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39 doing regression among different age groups, while the
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41 memory decline caused by SHS could be presented by the
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43 significant coefficient.
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56 The inconsistent conclusions between our studies and
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58 prior ones may probably due to the relatively simplified
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4 version of cognition test procedure in CHARLS
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6 questionnaires compared with the MoCA [23] and MMSE [24]. Some
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9 studies also used clinical or magnetic resonance imaging
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11 (MRI) evidence of neurologic damage to detect cognitive
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13 impairment [25]. Best adapted to a screening test, the MoCA
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15 exhibited excellent sensitivity in identifying MCI and AD
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17 (Alzheimer's disease) by 90% and 100%, respectively [26].
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22 The most popular hypothesis about the mechanisms
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24 underlying the links between SHS exposure and poorer
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26 cognitive performance lies in the notion that the carbon
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28 monoxide (CO) in tobacco smoke may interfere with the
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30 oxygen being delivered to the brain via the blood system.
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32 However, the reasons behind different effect on various
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34 domains of brain function are far from clear. One possible
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36 explanation derives from an animal research. Exposing
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38 animals to varying degrees of toxic mixtures of chemicals
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40 found in tobacco smoke may lead to reduced neuronal mass
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42 in specific regions of the brain associated with learning
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44 and memory. Since the hippocampal region of the brain is
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46 known to be involved in the mediation of memory [27] and
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48 learning, further research should be conducted in other
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50 regions dominating visuospatial and orientation ability.
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4 Another possible mechanism is that prolonged exposure to
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6 SHS may be a significant risk factor for cardiovascular
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8 disease (CVD)^[28], which may therefore lead to a range of
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10 health and cognitive problems in later life. A
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12 longitudinal design could elucidate this association by
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14 observing long-term exposure to SHS and a potential build-
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16 up of CVD as well as how these correlates with performance
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18 upon a range of cognitive measures.
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24 Several limitations need to be considered when
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26 interpreting this study and designing future studies.
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28 Firstly, the exposure to secondhand smoke was evaluated
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30 based on self-report measures. This might be subject to
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32 recall bias and lead to over-or-underestimation of exposure
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34^[8]. Therefore, further studies could include more
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36 biological assays, for example, cotinine residue levels or
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38 nicotine residue in saliva or hair samples^[29]. Previous
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40 research using serum cotinine as a biomarker of exposure
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42 to SHS found that higher levels of serum cotinine were
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44 associated with significant worse performance in reading,
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46 mathematics, and visual and spatial abilities in children
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48 and adolescents^[14]. However, no studies had used a
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50 combination of biomarker and self-report yet^[30]. Cognitive
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4 impairment could also be detected by the effect of
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6 apolipoprotein ε4 (Apo ε4) polymorphism, which was a known
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8 risk factor for dementia. Secondly, it may be impossible
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10 to control for all potentially confounding variables. After
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12 adjusting for age, household expenditure, education, area,
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14 chronic health condition and depressive symptoms, some
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16 other demographic or socioeconomic confounders may be
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18 neglected. Nevertheless, this did not appear to affect the
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20 magnitude of the association between SHS exposure and
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22 cognition ^[31]. Besides, the analyses only contained
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24 household SHS exposure, which precluded the analyses of the
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26 influence of environment smoke inhale on smoking proclivity.
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28 Whether exposure to household SHS can hasten the onset of
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30 cognitive impairment for older Chinese women could be
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32 further proved by running regression models in different
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34 age groups.
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49
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51

52 **Conflict of Interest**

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55 The authors have no conflicts of interest to declare.
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58 **Author's Contribution**

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4 Anying Bai wrote and participated in all aspects of this research, including the field
5
6 investigation. Dr Yangmu Huang reviewed and supervised this research. Yinzi Jin
7
8 participated in the statistical analysis of this work and reviewed the final article.
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11 **Data sharing statement**

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14 CHARLS data is available to the public online : <http://charls.pku.edu.cn>
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19 This is a self-funded research.
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Table 1. Characteristics of the Participants from 3 waves of CHARLS, 2011-2013-2015

Variable	2011-2013 (N=2802)		2011-2015 (N=2274)		2013-2015 (N=1799)	
	Count	Frequency	Count	Frequency	Count	Frequency
Area						
Urban	981	35.01%	730	32.10%	556	30.91%
Rural	1821	64.99%	1544	67.90%	1243	69.09%
Secondhand Smoke						
Less than 25 years	759	27.09%	531	23.35%	262	14.56%
More than 25 years and less than 30 years	634	22.63%	573	25.20%	385	21.40%
More than 30 years and less than 40 years	911	32.51%	800	35.18%	768	42.69%
More than 40 years	498	17.77%	370	16.27%	384	21.35%
Education						
Illiterate	1552	55.39%	1309	57.56%	1004	55.81%
Primary education	512	18.27%	414	18.21%	336	18.68%
Secondary or above	738	26.34%	551	24.23%	459	25.51%
Hypertension						
No hypertension	2124	75.80%	1720	75.64%	1365	75.88%
Hypertension with treatment	522	18.63%	1720	75.64%	358	19.90%
Hypertension without treatment	156	5.57%	130	5.72%	76	4.22%

Diabetes

No Diabetes in baseline	2643	94.33%	2140	94.11%	1704	94.72%
Have Diabetes with treatment	143	5.10%	120	5.28%	86	4.78%
Have Diabetes without treatment	16	0.57%	14	0.62%	9	0.50%

	Count	Mean (SD)	Count	Mean (SD)	Count	Mean (SD)
Age	2802	55.84 (8.22)	2274	56.19 (7.75)	1799	57.90 (7.43)
Annual Household Expenditure, yuan ^a	2802	13786.99 (14197.29)	2274	13060.14 (13639.33)	1799	16632.84 (18568.24)
Visuospatial ability ^b	2802	0.51 (0.50)	2274	0.48 (0.50)	1799	0.49 (0.50)
Orientation and attention ^c	2802	5.87 (3.29)	2274	5.84 (3.19)	1799	5.97 (3.14)
Memory Scores ^d	2802	3.33 (1.96)	2274	3.04 (1.93)	1799	3.15 (1.91)
Baseline Visuospatial ability	2802	0.57 (0.50)	2274	0.55 (0.50)	1799	0.54 (0.50)
Baseline Orientation and attention	2802	6.39 (2.92)	2274	6.25 (2.90)	1799	6.16 (3.00)
Baseline Memory Scores	2802	3.27 (1.98)	2274	3.23 (1.92)	1799	3.50 (1.78)
Baseline CES-D Score ^e	2802	12.09 (5.38)	2274	12.13 (5.45)	1799	10.90 (5.14)

Abbreviation: SHS, secondhand smoke.

a 1 US dollar = 6.3 yuan.

b The score range for visuospatial ability was 0-1.

c The score range for orientation and attention was 0-10. Higher scores indicate better mental status.

d The score range for episodic memory was 0-10. Higher scores indicate better memory function.

e A score of 10 or greater indicated the presence of depressive symptoms.

Table 2. Multivariable linear regression analysis of the relationship between smoking exposure and Visuospatial function and Orientation and Attention among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Visuospatial Scores			Orientation and Attention		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.01 ^a	-0.01, -0.00	-6.73	-0.02 ^a	-0.03, -0.01	-4.34
Expenditure	0.00	0.00, 0.00	0.01	0.00 ^a	0.00, 0.00	0.77
Secondhand Smoke Exposure^d						
25 to <30 years	-0.01	-0.04, 0.02	-0.72	0.05	-0.12, 0.21	0.56
≥30 to <40 years	-0.02	-0.05, 0.02	-0.95	-0.03	-0.20, 0.13	-0.38
≥ 40 years	-0.04 ^c	-0.08, 0.01	-1.67	-0.15	-0.38, 0.09	-1.24
Baseline Visuospatial Scores	0.23 ^a	0.21, 0.26	17.93			

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Baseline Orientation Scores					0.55 ^a	0.53, 0.57	44.86
Urban^e	0.06 ^a	0.04, 0.09	5.27		0.38 ^a	0.25, 0.51	5.72
Education^f							
Primary	0.23 ^a	0.20, 0.26	14.00		1.11 ^a	0.94, 1.27	12.91
Secondary or Above	0.29 ^a	0.26, 0.32	18.51		1.18 ^a	1.01, 1.36	13.44
Hypertension^g							
With Treatment	-0.03	-0.09, 0.02	-1.20		0.06	-0.24, 0.35	-0.38
Without Treatment	-0.02	-0.06, 0.03	-0.69		0.06	-0.11, 0.24	0.04
Missing Group	-0.05 ^c	-0.12, 0.01	-1.67		0.06	-0.19, 0.30	-0.01
Diabetes^h							
With Treatment	0.02	-0.03, 0.07	0.90		0.25 ^c	-0.03, 0.52	-1.77
Without Treatment	0.03	-0.04, 0.09	0.82		0.21	-0.06, 0.48	-0.23
Missing Group	0.07	-0.08, 0.21	0.88		0.50	-0.22, 1.23	0.67
Baseline CES-D Score	-0.00 ^c	-0.00, 0.00	-1.71		-0.02 ^b	-0.03, -0.00	-2.57
year = 2	-0.02	-0.04, 0.01	-1.58		0.09	-0.05, 0.22	1.29

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5 Abbreviations: CI, confidence interval; SHS, secondhand smoke.

6 a. $p < 0.01$

7 b. $p < 0.05$

8 c. $p < 0.1$

9 d. Referent: No SHS exposure or Less than 25 years.

10 e. Expenditure is expressed as the natural log of the annual household expenditure

11 f. Referent: Illiterate

12 g. Referent: Without hypertension

13 h. Referent: Without diabetes

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Table 3. Multivariable linear regression analysis of the relationship between smoking exposure and Episodic memory and Overall cognitive function among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Episodic Memory			Overall Cognition Scores		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.04 ^a	-0.05, -0.03	-11.37	-0.06 ^a	-0.07, -0.04	-7.87
Expenditure	0.00	0.00, 0.00	1.30	0.00 ^a	0.00, 0.00	0.32
Secondhand Smoke Exposure^d						
25 to <30 years	-0.04	-0.16, 0.08	-0.67	-0.01	-0.25, 0.25	-0.01
≥30 to <40 years	0.02	-0.09, 0.13	0.36	-0.05	-0.29, 0.19	-0.41
≥ 40 years	-0.16 ^b	-0.31, -0.01	-2.06	-0.33 ^a	-0.66, 0.01	-1.93
Baseline Memory Scores	0.30 ^a	0.28, 0.32	25.22			

Baseline Cognition Scores				0.55 ^a	0.46, 0.83	44.95
Urban^e	0.25 ^a	0.16, 0.34	5.60	0.65 ^a	0.46, 0.83	6.68
Education^f						
Primary	0.70 ^a	0.58, 0.80	12.42	1.77 ^a	1.53, 2.02	14.28
Secondary or Above	0.97 ^a	0.86, 1.08	17.29	2.00 ^a	1.74, 2.26	15.24
Hypertension^g						
With Treatment	0.04	-0.16, 0.23	0.35	0.13	-0.29, 0.56	0.62
Without Treatment	0.06	-0.06, 0.17	0.95	0.12	-0.14, 0.38	0.93
Missing Group	0.07	-0.12, 0.25	0.70	0.10	-0.27, 0.47	0.52
Diabetes^h						
With Treatment	-0.20 ^b	-0.38, 0.02	-2.20	-0.04	-0.43, 0.36	0.62
Without Treatment	-0.07	-0.25, 0.11	-0.77	0.08	-0.30, 0.47	0.43
Missing Group	0.32	-0.16, 0.80	1.30	0.87	-0.11, 1.84	1.75
Baseline CES-D Score	-0.01 ^b	-0.01, 0.00	-1.59	-0.01	-0.03, 0.00	-2.57
year = 2	-0.24	-0.33, -0.15	-5.21	-0.17	-0.37, 0.03	-1.70

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Constant	0.63	0.53, 0.74	11.54	6.48 ^a	5.59, 7.37	14.28
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Abbreviations: CI, confidence interval; SHS, secondhand smoke.

- a. p<0.01
- b. p<0.05
- c. p<0.1
- d. Referent: No SHS exposure or Less than 25 years.
- e. Expenditure is expressed as the natural log of the annual household expenditure
- f. Referent: Illiterate
- g. Referent: Without hypertension
- h. Referent: Without diabetes

For peer review only

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	12
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	12
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17
23				
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25
26 *Give information separately for exposed and unexposed groups.

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28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
32 available at <http://www.strobe-statement.org>.
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Exposure to Secondhand Smoke and Cognitive Function Among Middle-aged and Older Women in China: Findings of 3-waves of the China Health and Retirement Longitudinal Study

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Keywords:	EPIDEMIOLOGY, Dementia < NEUROLOGY, PUBLIC HEALTH

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1 **Title**

2 Exposure to Secondhand Smoke and Cognitive Function Among
3 Middle-aged and Older Women in China: Findings of 3-waves
4 of the China Health and Retirement Longitudinal Study

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7 Science Centre

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Abstract

Objectives: To examine the association between secondhand smoke and women's global cognitive function and cognitive subdomains.

Design: Cohort study

Participants: Data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS, 2011-2013-2015), and pooled analysis was applied to wave 1 and wave 2 (2011-2013), wave 2 and wave 3 (2013-2015) and wave 1 and wave 3 (2011-2015). Data from a total of 6875 Chinese women with normal cognitive function in baseline were selected for analysis, including 2981 who were interviewed in 2011, 2471 in 2013, and 1894 in 2015.

Main outcome measures and methods: Secondhand smoke was classified based on the length of exposed years (<25years, ≥25 to <30 years, ≥30 to <40 years, ≥40 years). Global cognitive function, visuospatial ability, orientation and attention, as well as episodic memory function were used as measures of cognitive function. Three waves of data were pooled by using dummy variable

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4 61 to differentiate between 2-year and 4-year. Lagged
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6 62 dependent variable models were used to examine
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9 63 independent associations between secondhand smoke and
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11 64 cognitive function. Demographic factors, socioeconomic
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14 65 factors, baseline cognitive functioning and health
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17 66 conditions were controlled in our models.

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19 67 **Results:** Secondhand smoke was found to be inversely and
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22 68 significantly associated with cognitive function.
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25 69 Compared with those had not been exposed to household
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27 70 secondhand smoke, women who had lived with a smoking
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30 71 husband had significantly faster cognition decline,
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33 72 especially in global cognitive function ($\beta=-0.33$, 95%CI=
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35 73 -0.66 to -0.01 , $P < 0.01$), visuospatial ability ($\beta=-0.04$,
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37 74 95%CI= -0.08 to -0.01 $P < 0.05$) and episodic memory
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40 75 function ($\beta=-0.16$, 95%CI= -0.31 to -0.01 $P = 0.031$).

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43 76 **Conclusions:** Household secondhand smoke exposure for more
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46 77 than 40 years was associated with a more significant
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49 78 decline in global cognitive function, visuospatial
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52 79 ability and episodic memory function, but not in
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55 80 orientation and attention function among older Chinese
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58 81 women.

59 82 **Key words:** ageing; passive smoking; panel analysis;
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4 83 visuospatial ability; memory
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7 84 **Strengths and limitations of this study:**
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9 85 ➤ This is the first study to investigate on the
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11 86 association between secondhand smoke exposure and
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13 87 women's different domains of cognitive functions in
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15 88 China by using a 4-year longitudinal national
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17 89 representative data.
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22 90 ➤ This study addressed the issue of reverse causation in observational cohort studies
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24 91 by used lagged dependent variable models and adjust for baseline cognition scores
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27 92 ➤ The exposure to secondhand smoke was evaluated based on
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29 93 self-report measures.
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32 94 ➤ The analyses only contained household SHS exposure and
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34 95 excluding environmental exposure.
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40 97 **Word Count: 3295**
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43 98 **Number of references:32**
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50 101 **Introduction**
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53 102 China's population has been ageing rapidly. By 2050,
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55 103 there will be 400 million Chinese citizens aged over 65
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57 104 years old, and 150 million of whom will be older than 80
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4 105 years old^[1]. It will become increasingly important to
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6 106 understand the cognitive changes that accompany ageing^[2].
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9 107 Cognitive impairment, described as a decline in
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11 108 intellectual functions^[3], ranges from mild forms of
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14 109 forgetfulness to severe and debilitating dementia ^[4]. The
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17 110 prevalence of cognitive impairment is rising, with national
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19 111 figures estimating that over 9.4% of older persons in China
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22 112 had cognitive impairment in 2011 ^[4].

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24 113 Numerous determinants such as environmental, individual,
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27 114 and genetic factors could favor evolution toward cognitive
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30 115 impairment, and both age and late-life hypertension
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33 116 increase the risk of dementia over time ^[5]. The mechanism
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36 117 lies in age-related functional and structural changes in
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38 118 cerebrovascular small and large blood vessels ^[6]. Besides
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41 119 chronic diseases factors, depression has long been known
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44 120 to affect memory and other neurocognitive domains. Previous
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47 121 studies have emphasized that depression could increase the
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50 122 risk of developing mild cognitive impairment (MCI) in
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53 123 cognitively normal elderly people^[7] .

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55 124 Exposure to secondhand smoke (SHS), also known as
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58 125 "passive smoking," refers to a situation where a never-
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126 smoker inhales another person's smoke either by exposure

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4 127 to sidestream smoke or mainstream smoke ^[8]. Current smoking
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6 128 prevalence in China decreased from 31.1% in 2002 to 28.1%
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9 129 in 2010; however, the number of adults exposed to SHS during
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11 130 this period still increased from 540 million to 556 million
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14 131 ^[2]. The negative health effects of high levels of exposure
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17 132 to SHS may be close to those of active smoking, including
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20 133 inferior performance on measures of general intelligence,
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22 134 visuospatial learning and memory and fine motor dexterity^[9]
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25 135 . Given the association between exposure to SHS and risk
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27 136 factors for cognitive impairment such as cardiovascular
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30 137 disease^[10] , hypertension^[11] , and stroke ^[12] , it is possible
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33 138 that high level of exposure may be a preventable risk factor
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35 139 for cognitive impairment or dementia ^[11, 13] .

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38 140 There are some evidence to suggest that older current
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40 141 smokers (ages ≥ 63) ^[14] or those being exposed to SHS (aged
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43 142 55-64) ^[13-16] were more likely to develop cognitive
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46 143 impairment compared with never-smokers. However, much less
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49 144 is known about whether and to what extent SHS is associated
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51 145 with global and subdomains of cognitive function among
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53 146 elder women in China. Previous studies in China indicated
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56 147 that SHS exposure increased the risk of cognitive
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59 148 impairment in older adults^[17, 18]. Nevertheless, both of
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4 149 these studies only used a 2-wave longitudinal data and did
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6 150 not control for baseline cognition^[17, 18]. Therefore, the
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9 151 primary aim of this study was to investigate the
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11 152 relationship between SHS and cognitive function among older
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14 153 non-smoking Chinese women, using a 3-wave longitudinal
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17 154 national representative data. Through the classification
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19 155 of respondents by different years of SHS exposure in a 4-
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22 156 year panel, we identified whether certain high SHS exposure
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25 157 groups were at higher risk of cognitive decline than others
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27 158 after controlling for confounders. Besides, we aimed to
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30 159 examine the association between SHS exposure and cognitive
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33 160 subdomains. This is especially important given the
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35 161 escalating ageing trend and increasing prevalence of SHS
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38 162 exposure in China.

163 **Methods**

164 **Data**

165 CHARLS had passed the ethical review before field investigation and we used data
166 from 3 waves of the China Health and Retirement Longitudinal Study (CHARLS,2011-
167 2013-2015), which was publicly available at <http://charls.pku.edu.cn>. CHARLS
168 involved participants with a nationally representative
169 survey of adults aged 45 years or older, as well as their
170 spouses when possible, and included assessments of social,

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4 171 economic, and health circumstances of community-residents.
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6 172 The national baseline survey was conducted between June
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9 173 2011 and March 2012 and samples were chosen through
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12 174 multistage probability sampling. After excluding empty or
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14 175 non-resident dwellings, final interviews were conducted on
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16
17 176 17,708 respondents from 10,257 households, which completed
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20 177 at least one module of the survey beyond the cover screening
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22 178 for age eligibility. CHARLS respondents were followed every
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25 179 2 years, using a face-to-face computer-assisted personal
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27 180 interview (CAPI) ^[14]. At baseline, there were 3381 married
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30 181 women who never smoked cigarettes and lived with spouses
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33 182 who had either smoked cigarettes in the past or smoked at
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35 183 the time of interview. Besides, all the data for each
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38 184 variable have been collected for those respondents. Our
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40 185 final sample was composed of 6875 respondents. Among them,
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43 186 2802 were interviewed again during the second wave of data
44
45
46 187 collection in 2013, and 2247 were interviewed again during
47
48 188 the third wave in 2015. The similar sample selection
49
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51 189 process was conducted for participants in the second wave
52
53 190 in 2013 as a baseline. The final sample consisted of 1799
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56 191 women who were investigated again in 2015 as participants.

192 **Measures**

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4 193 ***Secondhand Smoke***
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6 194 In this study, the exposure to SHS among Chinese women
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9 195 was assessed through several surveys based on standardized
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11 196 CHARLS questionnaire. Questions about the participant's
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14 197 current marital status, the exact year they got married,
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17 198 and the year the husband in each household has begun or
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19 199 ceased smoking at home were asked.
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22 200 The smoking status section contained four questions:
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24 201 "Have you ever chewed tobacco, smoked a pipe, smoked self-
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26 202 rolled cigarettes, or smoked cigarettes/cigars?", "Do you
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28 203 still have the habit or have you totally quit?", "At what
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30 204 age did you totally quit smoking?" and "At what age did you
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32 205 start to smoke on a regular basis?". If the answer to the
33
34 206 first question was "yes", they were defined as "current
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36 207 smokers". Our analysis of SHS exposure focused only on
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38 208 never smokers excluding the "current smokers", because of
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40 209 the difficulty to differentiate the negative effects of
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42 210 active smoking on health condition from that of SHS
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44 211 exposure. The length of SHS exposure was calculated and
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46 212 expressed as the total number of years that never-smoking
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48 213 women spent living with their spouses who smoked cigarettes
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50 214 at home.
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215 Since the impact of SHS might be neglected if we only
216 used a continuous variable to represent exposure; moreover,
217 compared with continuous variables, the use of categorical
218 variables has greater public health significance. Based on
219 the constructed SHS exposure variable, the participants
220 were classified into four different groups: Never or being
221 exposed to SHS for less than 25 years, more than 25 years
222 and less than 30 years, more than 30 years and less than
223 40 years and over 40 years.

224 ***Cognitive function***

225 The cognitive function of the respondents in CHARLS
226 questionnaires was measured through a question-and-answer
227 interview instrument, and the respondents were followed
228 every two years using a face-to-face, computer-aided
229 personal interview (CAPI). These various sections of the questionnaire
230 could assess cognitive subdomains including visuospatial ability, orientation and
231 attention, and episodic memory. Figure drawing was tested by asking the participants
232 to reproduce a picture of two overlapped pentagons in CHARLS questionnaires^[18]. It
233 was used to measure a person's ability to identify visual and spatial relationships among
234 objects. The Telephone Interview of Cognitive Status (TICS)
235 was a screening test, including serial subtractions of 7
236 from 100 (up to 5 times), date (month, day, and year and

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4 237 season), and the day of the week. In order to assess orientation and
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6 238 attention function, the number of correct answers to the above questions in TICS was
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9 239 scored and summed up (range 0 to 10). Participants who successfully completed the
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11 240 task received a score of 1, and those who failed received 0^[19].

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14 241 In addition, the word recall test was consisted of 2
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16 242 components, immediate recall and delayed recall, and
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18 243 evaluated episodic memory. Participants were required to
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20 244 repeat 10 Chinese nouns just read to them immediately, and
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22 245 after 20 questions concerning Center for Epidemiologic
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24 246 Studies Depression Scale (CES-D, approximately 4 to 10
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26 247 minutes), they were again asked to recall as many of the
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28 248 original words as possible. The item was coded as 1 if
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30 249 recalled by the respondent, and as 0 if not. Scores for
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32 250 immediate and delayed recall both varied from 0 to 10. An
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34 251 evaluated episodic memory score was calculated using the
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36 252 mean of scores in immediate and delayed word recall (range
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38 253 0 to 10)^[19].

39
40 254 The overall cognition scores were the sum of the three
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42 255 different domains (range 0 to 21).

256 ***Control variables***

257 Given that cognitive function may vary across
258 demographic and socioeconomic status, we thus included age,
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260

259 urban/rural residence, education, annual household
260 expenditures, chronic diseases and depressive symptoms as
261 control variables. Education was categorized into 3 groups:
262 "illiterate", "primary education" and "secondary education
263 or above". Arterial hypertension and diabetes mellitus are
264 separately strong independent risk factors for the
265 development of cognitive impairment and dementia^[20] ^[21].
266 Thus, the baseline chronic disease of hypertension and
267 diabetes were classified as three types based on self-
268 reported conditions on whether the participants were being
269 treated: having hypertension/diabetes with treatment,
270 having hypertension/diabetes without treatment and not
271 having hypertension/diabetes. The measure of depressive
272 symptoms was based on the 10-item version of the CES-D
273 short form, and each of the 4-option response to the item
274 was scored ranging from 0 to 3. The total score is the sum
275 of points for all 10 items, and a score of 10 or higher
276 suggests the presence of depressive symptoms ^[6].

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278 ***Patient and Public Involvement***

279 No patient involved.

280 **Analysis**

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4 281 All analyses were conducted with STATA, version 14.0
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6 282 (Stata, College Station, TX, USA). The lagged dependent-
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9 283 variable regression models with ordinary least squares
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11 284 estimation were used during analysis. LDV models were
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14 285 superior for analyzing the effects of predictor variables
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17 286 on an outcome with 2-wave panel data while controlling for
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19 287 the influence of time-invariant variables^[22]. It adjusted
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22 288 for baseline cognitive conditions for all participants,
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25 289 therefore provided more robust estimates of the effects of
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27 290 independent variables. After pooling the three sets of
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30 291 panel data into one through using the "year" dummy variable
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33 292 to differentiate between a change in 2 years or in 4 years,
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35 293 we have 6875 respondents who have complete data on all
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37 294 variables. The overall cognitive scores, episodic memory
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39 295 scores, visuospatial ability scores and orientation and
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41 296 attention scores were 4 separate outcome variables. The
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43 297 different groups of SHS exposure years were the predictor
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45 298 variable, and other independent variables included all
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47 299 demographic and socioeconomic characteristics. Prior to
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49 300 fitting the regression models, descriptive analyses were
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51 301 conducted to estimate the mean and standard deviations for
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53 302 continuous data and frequencies and percentages for
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4 303 categorical data.
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8 305 **Results**
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10 306 Table 1 provides a descriptive summary of all the
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12 307 variables for participants from each panel of three
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14 308 different waves: 2011-2013, 2011-2015 and 2013-2015. High
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16 309 prevalence of SHS exposure between 30 to 40 years was seen
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18 310 in different panels, accounting for 32.51%, 35.18% and
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20 311 42.69% respectively.
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26 312 The participants were over 45 years old, with the mean
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28 313 age of 56, 56 and 58 years old, respectively in those waves.
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30 314 Participants were more likely to live in a rural area, have
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32 315 a lower education background and do not have hypertension
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34 316 or diabetes diagnoses at baseline. In addition, our results
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36 317 indicated that the mean baseline cognition scores were
37
38 318 higher than cognition scores after 2 or 4 years. The mean
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40 319 scores of CES-D suggested that the prevalence of depression
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42 320 among Chinese middle-aged and old-aged women was increased
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44 321 in those years. Other socio-demographic characteristics of
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46 322 the respondents are shown in Table 1
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54 323 Results from the regression models for the
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56 324 relationship between SHS exposure and each domain of the
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58 325 cognitive function and overall cognition scores are
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4 326 reported in Table 2 and Table 3. Scores of episodic
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6 327 memory, orientation and attention and visuospatial among
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9 328 respondents at baseline were strong predictors of their
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11 329 corresponding cognitive function measures after 2 or 4
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14 330 years. Based on the analysis adjusted for age, annual
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17 331 household expenditure, education, baseline cognitive
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19 332 function and another chronic health status, we found that
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22 333 only being exposed to SHS for more than 40 years was
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25 334 significantly associated with a decline in visuospatial
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27 335 abilities, episodic memory and overall cognition scores
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30 336 for all respondents. Compared with respondents who were
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33 337 not exposed to SHS or exposed to it for less than 25
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36 338 years, those who have been exposed to SHS for more than
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38 339 40 years was associated with a 0.04-point decline in
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40 340 visuospatial abilities (95%CI, -0.08 to -0.01 P <0.1), a
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42 341 0.16-point decline in episodic memory (95%CI, -0.31 to -
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44 342 0.01 P <0.05), and a 0.33-point decline in overall
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47 343 cognition function (95%CI, -0.66 to -0.01 P <0.01). In
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50 344 addition, age was also negatively associated with
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53 345 cognitive function. Each one-year older was associated
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56 346 with 0.01-point, 0.01-point, 0.03-point, and 0.05-point
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59 347 decrease in visuospatial (95%CI, -0.01 to -0.00 P <0.01),
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4 348 orientation (95%CI, -0.03 to -0.01 P <0.01), memory
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6 349 (95%CI, -0.31 to -0.01 P <0.05) and overall cognition
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9 350 scores (95%CI, -0.66 to -0.01 P <0.01), respectively.
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11 351 High education level was associated with better cognitive
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14 352 performance, especially in orientation and attention. In
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17 353 addition, a one-point increase in CESD scores was
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19 354 associated with 0.02-point decrease in scores of
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22 355 orientation and attention (95%CI, -0.03 to 0.00 P <0.05),
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25 356 showing that respondents with depressive symptoms were
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27 357 more likely to demonstrate a cognitive decline in
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30 358 specific functions.

359 **Discussion**

360 Results from this longitudinal study with a large,
361 representative sample of middle-aged and older women in
362 China indicated that exposure to SHS for over 40 years was
363 significantly associated with the more unsatisfactory
364 performance of global cognition and cognitive subdomains.
365 It is the first examination of cognitive subdomains
366 concerning household SHS exposure using a 4-year
367 longitudinal data in China. The inferior performance of SHS
368 on visuospatial abilities, episodic memory and orientation
369 and attention abilities are novel. Because these domains

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4 370 were not specifically evaluated in earlier studies among
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6 371 middle-aged and older women who never smoke. In addition
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9 372 to the previous findings that SHS was associated with poor
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11 373 cognitive performance, especially in children, adolescents
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14 374 and adults ^[18]. We found that having a high educational
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16 375 level, living in an urban area and having better baseline
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18 376 cognitive function would improve their cognitive
19
20 377 performance. The episodic memory score of participants with
21
22 378 diabetes at baseline decreased by 0.172 points compared
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24 379 with those without diabetes, which is similar to previous
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26 380 findings^[9].

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32 381 Moreover, our results showed that compared with women
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34 382 who have never been exposed to SHS or have been exposed for
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36 383 less than 20 years, those who have been exposed to SHS for
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38 384 more than 40 years have a significant decline in
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40 385 visuospatial function (0.04-point), episodic memory (0.16-
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42 386 point) and overall cognitive scores (0.33-point). These
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44 387 findings were quite similar in magnitude to prior research
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46 388 on the relationship between SHS and cognitive function ^[14].
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48 389 Moheet and colleagues (2015) conducted a cross-sectional
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50 390 study in the North East of England to explore the impact
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52 391 of diabetes on cognitive function and brain structure
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4 392 (N=150). Research suggested that compared with non-exposed
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6 393 people, participants who had no history of smoking and
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9 394 being averagely exposed to SHS for around 6 years showed
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11 395 significantly reduced performance in processing speed (i.e.
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14 396 how quickly one can process information and perform tasks)
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16
17 397 and executive function (i.e. the ability to organize memory,
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19 398 cognitive flexibility, and problem-solving ability)^[22].
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21
22 399 Another longitudinal ageing study in China (N=4809, ages
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24 400 ≥50) found that never smokers exposed to the highest levels
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27 401 of SHS (salivary cotinine concentrations 0.8-13.5 ng/ml)
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30 402 were more likely to be cognitively impaired (odds ratio
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32 403 =1.70) than those exposed to little or no SHS^[18].

35 404 Attention referred to the ability to concentrate and
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37 405 focus on specific stimuli slightly declined in later life
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40 406 ^[13]. Orientation was one's ability to identify the exact
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43 407 date, month, day and season of the year^[23]. Our results
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46 408 suggested that for each one-year increase in age, there
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48 409 were additional 0.01-point, 0.02-point, 0.04-point and
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51 410 0.06-point decline in visuospatial, orientation, memory and
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53 411 overall cognition scores, respectively. SHS seems to be
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56 412 more strongly associated with cognitive decline than ageing,
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58 413 since the magnitude of significant coefficient between
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4 414 SHS and cognitive decline was almost four times the one in
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6 415 ageing. However, the relationship between SHS and
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9 416 orientation and attention ability was not observed. This
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11 417 may due to the size of the sample is relatively small, plus
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14 418 the period of cohort study after controlling for all
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17 419 demographic and socioeconomic confounders is relatively
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20 420 short.

21
22 421 Visuospatial abilities involve the ability to understand
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24 422 space in two and three dimensions. In our study, an inversed
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27 423 relationship between SHS exposure and visuospatial
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30 424 abilities among middle-aged and older adults was presented,
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32 425 showing a 0.04-point decline in their visuospatial scores.
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34
35 426 Such an inversed relationship between SHS exposure and
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38 427 visuospatial reasoning skills was also reported among
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40 428 American children (N=5683; ages 6-16), showing that years
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43 429 of SHS exposure was significantly associated with lower
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46 430 scores for reading, math, and visuospatial skills, after
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48 431 adjusting for covariates ^[15]. As one of the most common
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51 432 cognitive complaints among elders, episodic memory refers
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53 433 to personally experienced events which could be measured
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56 434 by stories, word lists or figures. Previous research has
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58 435 indicated that the onset of memory decline may vary among
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4 436 different memory types, with episodic memory decline
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6 437 possibly being lifelong [24]. Our study could not explore
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9 438 the onset age of memory decline without doing regression
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11 439 among different age groups. The significant coefficient
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14 440 could indicate memory decline associated with SHS exposure.

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17 441 The inconsistent conclusions between our studies and
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19 442 prior ones may probably due to the relatively simplified
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21
22 443 version of the cognition test procedure in CHARLS
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25 444 questionnaires compared with the MoCA [14] and MMSE [25]. Some
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27 445 studies also used clinical or magnetic resonance imaging
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30 446 (MRI) evidence of neurologic damage to detect cognitive
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33 447 impairment. Best adapted to a screening test, the MoCA
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35 448 exhibited excellent sensitivity in identifying MCI and AD
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38 449 (Alzheimer's disease) by 90% and 100%, respectively [26].

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40 450 The most popular hypothesis about the mechanisms
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43 451 underlying the links between SHS exposure and more
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46 452 unsatisfactory cognitive performance lies in the notion
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49 453 that the carbon monoxide (CO) in tobacco smoke may
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52 454 interfere with the oxygen being delivered to the brain via
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55 455 the blood system. However, the reasons behind the
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58 456 different effect on various domains of brain function are
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60 457 far from clear. One possible explanation derives from

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4 458 research on laboratory animals. Exposing animals to
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6 459 varying degrees of toxic mixtures of chemicals found in
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9 460 tobacco smoke may lead to reduced neuronal mass in specific
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11 461 regions of the brain associated with learning and memory.
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14 462 Since the hippocampal region of the brain is known to be
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16 463 involved in the mediation of memory [27] and learning,
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18 464 further research should be conducted in other regions
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20 465 dominating visuospatial and orientation ability. Another
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22 466 possible mechanism is that prolonged exposure to SHS may
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24 467 be a significant risk factor for cardiovascular disease
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26 468 (CVD) [28], which may therefore lead to a range of health
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28 469 and cognitive problems in later life. In the future, a
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30 470 longitudinal design may elucidate any associations by
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32 471 observing long-term exposure to SHS and the incidence of
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34 472 CVD, and whether this CVD may mediate or interact with SHS
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36 473 exposure to impact cognitive function.
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38 474 Several limitations need to be considered when interpreting
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40 475 this study and designing future studies. Firstly, exposure
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42 476 to SHS was evaluated based on self-report measures. This
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44 477 might be subject to recall bias and lead to over-or-
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46 478 underestimation of exposure [29]. Therefore, further studies
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48 479 could include more biological assays, for example, cotinine
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4 480 residue levels or nicotine residue in saliva or hair
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6 481 samples ^[30]. Previous research using serum cotinine as a
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9 482 biomarker of exposure to SHS found that higher levels of
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11 483 serum cotinine were associated with significantly worse
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14 484 performance in reading, mathematics, and visual and spatial
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17 485 abilities in children and adolescents ^[8]. However, no
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19 486 studies had used a combination of biomarker and self-report
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22 487 yet ^[31]. Some validated biomarkers could be used as proxies
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25 488 for AD neuropathological changes, such as cerebrospinal
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27 489 fluid (CSF) amyloid-beta (A β)42 concentrations or A β 42/
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30 490 A β 40 ratio and amyloid load on positron emission tomography
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33 491 (PET) scans. These biomarkers could provide more reliable
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35 492 measures of cognitive impairment^[32]. Secondly, it may be
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38 493 impossible to control for all potentially confounding
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41 494 variables. After adjusting for age, household expenditure,
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43 495 education, area, chronic health condition and depressive
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46 496 symptoms, some other demographic or socioeconomic
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49 497 confounders may be neglected. However, this did not appear
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52 498 to affect the magnitude of the association between SHS
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54 499 exposure and cognition ^[14]. Besides, the analyses only
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56 500 contained household SHS exposure, which precluded the
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59 501 analyses of the influence of environment smoke inhale on
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4 502 smoking proclivity. Whether exposure to household SHS can
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6 503 hasten the onset of cognitive impairment for older Chinese
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9 504 women could be further proved by running regression models
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12 505 in different age groups.

13 14 506 **Acknowledgments :**

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18
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20 21 22 509 **Conflict of Interest**

23
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25 510 The authors have no conflicts of interest to declare.

26 27 511 **Author's Contribution**

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30 512 Anying Bai wrote and participated in all aspects of this research, including the field
31
32 513 investigation. Dr Yangmu Huang reviewed and supervised this research. Yinzi Jin
33
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35 514 participated in the statistical analysis of this work and reviewed the final article.

36 37 515 **Data sharing statement**

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40 516 CHARLS data is available to the public online: <http://charls.pku.edu.cn>

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44
45 518 This is a self-funded research.

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48 49 520 **Reference**

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Table 1. Characteristics of the Participants from 3 waves of CHARLS, 2011-2013-2015

Variable	2011-2013 (N=2802)		2011-2015 (N=2274)		2013-2015 (N=1799)	
	Count	Frequency	Count	Frequency	Count	Frequency
Area						
Urban	981	35.01%	730	32.10%	556	30.91%
Rural	1821	64.99%	1544	67.90%	1243	69.09%
SHS						
Less than 25 years	759	27.09%	531	23.35%	262	14.56%
More than 25 years and less than 30 years	634	22.63%	573	25.20%	385	21.40%
More than 30 years and less than 40 years	911	32.51%	800	35.18%	768	42.69%
More than 40 years	498	17.77%	370	16.27%	384	21.35%
Education						
Illiterate	1552	55.39%	1309	57.56%	1004	55.81%
Primary education	512	18.27%	414	18.21%	336	18.68%
Secondary or above	738	26.34%	551	24.23%	459	25.51%
Hypertension						
No hypertension	2124	75.80%	1720	75.64%	1365	75.88%
Hypertension with treatment	522	18.63%	1720	75.64%	358	19.90%
Hypertension without treatment	156	5.57%	130	5.72%	76	4.22%
Diabetes						
No Diabetes in baseline	2643	94.33%	2140	94.11%	1704	94.72%

Have Diabetes with treatment	143	5.10%	120	5.28%	86	4.78%
Have Diabetes without treatment	16	0.57%	14	0.62%	9	0.50%
	Count	Mean (SD)	Count	Mean (SD)	Count	Mean (SD)
Age	2802	55.84 (8.22)	2274	56.19 (7.75)	1799	57.90 (7.43)
Annual Household Expenditure, yuan ^a	2802	13786.99 (14197.29)	2274	13060.14 (13639.33)	1799	16632.84 (18568.24)
Visuospatial ability ^b	2802	0.51 (0.50)	2274	0.48 (0.50)	1799	0.49 (0.50)
Orientation and attention ^c	2802	5.87 (3.29)	2274	5.84 (3.19)	1799	5.97 (3.14)
Memory Scores ^d	2802	3.33 (1.96)	2274	3.04 (1.93)	1799	3.15 (1.91)
Baseline Visuospatial ability	2802	0.57 (0.50)	2274	0.55 (0.50)	1799	0.54 (0.50)
Baseline Orientation and attention	2802	6.39 (2.92)	2274	6.25 (2.90)	1799	6.16 (3.00)
Baseline Memory Scores	2802	3.27 (1.98)	2274	3.23 (1.92)	1799	3.50 (1.78)
Baseline CES-D Score ^e	2802	12.09 (5.38)	2274	12.13 (5.45)	1799	10.90 (5.14)

Abbreviation: SHS, secondhand smoke.

a 1 US dollar = 6.3 yuan.

b The score range for visuospatial ability was 0-1.

c The score range for orientation and attention was 0-10. Higher scores indicate better mental status.

d The score range for episodic memory was 0-10. Higher scores indicate better memory function.

e A score of 10 or greater indicated the presence of depressive symptoms.

Table 2. Adjusted Multivariable linear regression analysis of the relationship between smoking exposure and Visuospatial function and Orientation and Attention among older Chinese women (N = 6875), 2011–2013–2015

VARIABLES	Visuospatial Function			Orientation and Attention		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.01 ^a	-0.01, -0.00	-6.73	-0.02 ^a	-0.03, -0.01	-4.34
Expenditure	0.00	0.00, 0.00	0.01	0.00 ^a	0.00, 0.00	0.77
SHS Exposure^d						
25 to <30 years	-0.01	-0.04, 0.02	-0.72	0.05	-0.12, 0.21	0.56
≥30 to <40 years	-0.02	-0.05, 0.02	-0.95	-0.03	-0.20, 0.13	-0.38
≥ 40 years	-0.04 ^c	-0.08, 0.01	-1.67	-0.15	-0.38, 0.09	-1.24
Baseline Visuospatial Function	0.23 ^a	0.21, 0.26	17.93			
Baseline Orientation and Attention				0.55 ^a	0.53, 0.57	44.86

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Urban^e	0.06 ^a	0.04, 0.09	5.27	0.38 ^a	0.25, 0.51	5.72
Education^f						
Primary	0.23 ^a	0.20, 0.26	14.00	1.11 ^a	0.94, 1.27	12.91
Secondary or Above	0.29 ^a	0.26, 0.32	18.51	1.18 ^a	1.01, 1.36	13.44
Hypertension^g						
With Treatment	-0.03	-0.09, 0.02	-1.20	0.06	-0.24, 0.35	-0.38
Without Treatment	-0.02	-0.06, 0.03	-0.69	0.06	-0.11, 0.24	0.04
Missing Group	-0.05 ^c	-0.12, 0.01	-1.67	0.06	-0.19, 0.30	-0.01
Diabetes^h						
With Treatment	0.02	-0.03, 0.07	0.90	0.25 ^c	-0.03, 0.52	-1.77
Without Treatment	0.03	-0.04, 0.09	0.82	0.21	-0.06, 0.48	-0.23
Missing Group	0.07	-0.08, 0.21	0.88	0.50	-0.22, 1.23	0.67
Baseline CES-D Score	-0.00 ^c	-0.00, 0.00	-1.71	-0.02 ^b	-0.03, -0.00	-2.57
year = 2	-0.02	-0.04, 0.01	-1.58	0.09	-0.05, 0.22	1.29

Abbreviations: CI, confidence interval; SHS, secondhand smoke.

a. p<0.01

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5 b. $p < 0.05$

6 c. $p < 0.1$

7 d. Referent: No SHS exposure or Less than 25 years.

8 e. Expenditure is expressed as the natural log of the annual household expenditure

9 f. Referent: Illiterate

10 g. Referent: Without hypertension

11 h. Referent: Without diabetes

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14 I. This model adjusted for age, expenditure, living area, education, baseline hypertension, diabetes, depression status and baseline cognitive function.

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Table 3. Adjusted Multivariable linear regression analysis of the relationship between smoking exposure and Episodic memory and Overall cognitive function among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Episodic Memory			Overall Cognition		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.04 ^a	-0.05, -0.03	-11.37	-0.06 ^a	-0.07, -0.04	-7.87
Expenditure	0.00	0.00, 0.00	1.30	0.00 ^a	0.00, 0.00	0.32
SHS Exposure^d						
25 to <30 years	-0.04	-0.16, 0.08	-0.67	-0.01	-0.25, 0.25	-0.01
≥30 to <40 years	0.02	-0.09, 0.13	0.36	-0.05	-0.29, 0.19	-0.41
≥ 40 years	-0.16 ^b	-0.31, -0.01	-2.06	-0.33 ^a	-0.66, 0.01	-1.93
Baseline Episodic Memory	0.30 ^a	0.28, 0.32	25.22			
Baseline Overall Cognition				0.55 ^a	0.46, 0.83	44.95

Urban^e	0.25 ^a	0.16, 0.34	5.60	0.65 ^a	0.46, 0.83	6.68
Education^f						
Primary	0.70 ^a	0.58, 0.80	12.42	1.77 ^a	1.53, 2.02	14.28
Secondary or Above	0.97 ^a	0.86, 1.08	17.29	2.00 ^a	1.74, 2.26	15.24
Hypertension^g						
With Treatment	0.04	-0.16, 0.23	0.35	0.13	-0.29, 0.56	0.62
Without Treatment	0.06	-0.06, 0.17	0.95	0.12	-0.14, 0.38	0.93
Missing Group	0.07	-0.12, 0.25	0.70	0.10	-0.27, 0.47	0.52
Diabetes^h						
With Treatment	-0.20 ^b	-0.38, 0.02	-2.20	-0.04	-0.43, 0.36	0.62
Without Treatment	-0.07	-0.25, 0.11	-0.77	0.08	-0.30, 0.47	0.43
Missing Group	0.32	-0.16, 0.80	1.30	0.87	-0.11, 1.84	1.75
Baseline CES-D Score	-0.01 ^b	-0.01, 0.00	-1.59	-0.01	-0.03, 0.00	-2.57
year = 2	-0.24	-0.33, -0.15	-5.21	-0.17	-0.37, 0.03	-1.70

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Constant	0.63	0.53, 0.74	11.54	6.48 ^a	5.59, 7.37	14.28
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- Abbreviations: CI, confidence interval; SHS, secondhand smoke.
- a. p<0.01
 - b. p<0.05
 - c. p<0.1
 - d. Referent: No SHS exposure or Less than 25 years.
 - e. Expenditure is expressed as the natural log of the annual household expenditure
 - f. Referent: Illiterate
 - g. Referent: Without hypertension
 - h. Referent: Without diabetes
 - I. This model adjusted for age, expenditure, living area, education, baseline hypertension, diabetes, depression status and baseline cognitive function.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	12
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17
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26 *Give information separately for exposed and unexposed groups.

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28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
32 available at <http://www.strobe-statement.org>.
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BMJ Open

The impact of secondhand smoke exposure on cognitive function among middle-aged and older women in China: Findings from 3-waves of the China Health and Retirement Longitudinal Study

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Secondary Subject Heading:	Smoking and tobacco, Public health, Mental health
Keywords:	EPIDEMIOLOGY, Dementia < NEUROLOGY, PUBLIC HEALTH

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4 1 **Title**

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6 2 The impact of secondhand smoke exposure on cognitive
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9 3 function among middle-aged and older women in China:
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11 4 Findings from 3-waves of the China Health and Retirement
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13 5 Longitudinal Study

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16 6 Anying, Bai ¹, Yinzi Jin Ph.D.¹, Yangmu Huang Ph.D.¹

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11
12 **Abstract**
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14 **Objectives:** To examine the association between secondhand
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17 smoke and women's global cognitive function and cognitive
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19 subdomains.
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22 **Design:** Cohort study
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25 **Participants:** Data for this study were obtained from the
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27 China Health and Retirement Longitudinal Study (CHARLS,
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29 2011-2013-2015), and pooled analysis was applied to wave
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31 1 and wave 2 (2011-2013), wave 2 and wave 3 (2013-2015)
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33 and wave 1 and wave 3 (2011-2015). Data from a total of
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35 6875 Chinese women with normal cognitive function at
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38 baseline were selected for analysis, including 2981 who
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41 were interviewed in 2011, 2471 in 2013, and 1894 in 2015.
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45 **Main outcome measures and methods:** Secondhand smoke (SHS) was
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48 classified based on the number of exposed years
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50 (<25years, ≥25 to <30 years, ≥30 to <40 years, ≥40
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52 years). Global cognitive function, visuospatial ability,
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54 orientation and attention, as well as episodic memory
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56 function were used as measures of cognitive function.
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4 61 Three waves of data were pooled by using a dummy variable
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6 62 to differentiate between 2-year and 4-year groups. Lagged
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9 63 dependent variable models were used to examine
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11 64 independent associations between secondhand smoke and
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14 65 cognitive function. Demographic factors, socioeconomic
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17 66 factors, baseline cognitive functioning and health
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19 67 conditions were controlled for in our models.

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22 68 **Results:** Secondhand smoke was found to be inversely and
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25 69 significantly associated with cognitive function.
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27 70 Compared with those had not been exposed to household
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30 71 secondhand smoke, women who had lived with a smoking
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33 72 husband had a significantly faster cognition decline,
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35 73 especially in global cognitive function ($\beta=-0.33$, 95%CI=
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37 74 -0.66 to -0.01 , $P < 0.01$), visuospatial ability ($\beta=-0.04$,
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39 75 95%CI= -0.08 to -0.01 $P < 0.05$) and episodic memory
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42 76 function ($\beta=-0.16$, 95%CI= -0.31 to -0.01 $P = 0.031$).

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45 77 **Conclusions:** Household secondhand smoke exposure for more
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48 78 than 40 years was associated with a more significant
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51 79 decline in global cognitive function, visuospatial
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53 80 ability and episodic memory function, but not in
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56 81 orientation and attention function among older Chinese
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58 82 women.
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83 **Key words:** ageing; passive smoking; panel analysis;

84 visuospatial ability; memory

85 **Strengths and limitations of this study:**

86 ➤ This is the first study to investigate the association
87 between secondhand smoke exposure and different domains
88 of women's cognitive function in China by using 4-year
89 of longitudinal national representative data.

90 ➤ This study addressed the issue of reverse causation in observational cohort studies
91 by used lagged dependent variable models and adjust for baseline cognition scores

92 ➤ The exposure to secondhand smoke was evaluated based on
93 self-reported measures.

94 ➤ The analyses only contained household SHS exposure and
95 excluded environmental exposure.

97 **Word Count: 3352**

98 **Number of references:32**

99 **Number of data elements:1**

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101 **Introduction**

102 China's population has been ageing rapidly. By 2050,
103 there will be 400 million Chinese citizens aged over 65
104 years old, 150 million of whom will be older than 80 years

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4 105 old^[1]. It will become increasingly important to understand
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6 106 the cognitive changes that accompany ageing^[2]. Cognitive
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9 107 impairment, described as a decline in intellectual
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11 108 function^[3], ranges from mild forms of forgetfulness to
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14 109 severe and debilitating dementia ^[4]. The prevalence of
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17 110 cognitive impairment is rising, with national figures
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19 111 estimating that over 9.4% of older persons in China had
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22 112 cognitive impairment in 2011 ^[4].

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25 113 Numerous determinants such as environmental, individual,
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27 114 and genetic factors could favor evolution toward cognitive
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30 115 impairment, and both age and late-life hypertension
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32 116 increase the risk of dementia over time ^[5]. The mechanism
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35 117 lies in age-related functional and structural changes in
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37 118 cerebrovascular small and large blood vessels ^[6]. Besides
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40 119 chronic diseases factors, depression has long been known
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42 120 to affect memory and other neurocognitive domains. Previous
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45 121 studies have emphasized that depression could increase the
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48 122 risk of developing mild cognitive impairment (MCI) in
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51 123 cognitively normal elderly people^[7] .

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53 124 Exposure to secondhand smoke (SHS), also known as
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56 125 "passive smoking," refers to a situation where a never-
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59 126 smoker inhales another person's smoke either by exposure
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4 127 to sidestream smoke or mainstream smoke ^[8]. Current smoking
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6 128 prevalence in China has decreased from 31.1% in 2002 to
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9 129 28.1% in 2010; however, the number of adults exposed to SHS
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11 130 during this period still increased from 540 million to 556
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14 131 million due to population growth ^[2]. The negative health
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17 132 effects of high levels of exposure to SHS may be close to
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20 133 those of active smoking, including inferior performance on
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22 134 measures of general intelligence, visuospatial learning and
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25 135 memory and fine motor dexterity^[9]. Given the association
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27 136 between exposure to SHS and risk factors for cognitive
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30 137 impairment such as cardiovascular disease^[10],
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32 138 hypertension^[11], and stroke ^[12], it is possible that a high
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35 139 level of exposure may be a preventable risk factor for
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38 140 cognitive impairment or dementia ^[11, 13].

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40 141 There is some evidence to suggest that older current
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42 142 smokers (ages ≥ 63) ^[14] or those being exposed to SHS (aged
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44 143 55–64) ^[13–16] were more likely to develop cognitive
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47 144 impairment compared with never-smokers. However, much less
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50 145 is known about whether and to what extent, SHS is associated
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52 146 with global and subdomains of cognitive function among
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55 147 elder women in China. Previous studies in China indicated
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58 148 that SHS exposure increased the risk of cognitive
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4 149 impairment in older adults^[17, 18]. Nevertheless, both of
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6 150 these studies only used 2-wave longitudinal data and did
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9 151 not control for baseline cognition^[17, 18]. Therefore, the
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11 152 primary aim of this study was to investigate the
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13 153 relationship between SHS and cognitive function among older
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15 154 non-smoking Chinese women, using a 3-wave longitudinal
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17 155 national representative data. Through the classification
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19 156 of respondents by different years of SHS exposure in a 4-
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21 157 year panel, we identified whether certain high SHS exposure
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23 158 groups were at higher risk of cognitive decline than others
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25 159 after controlling for confounders. Besides, we aimed to
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27 160 examine the association between SHS exposure and cognitive
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29 161 subdomains. This is especially important given the growing
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31 162 and ageing population, and increasing prevalence of SHS
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33 163 exposure in China.
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43 **Methods**

44 **Data**

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46 165 CHARLS had passed the ethical review before field investigation and we used data
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48 166 from 3 waves of the China Health and Retirement Longitudinal Study (CHARLS,2011-
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50 167 2013-2015), which was publicly available at <http://charls.pku.edu.cn>. CHARLS
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52 168 involved participants with a nationally representative
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54 169 survey of adults aged 45 years or older, as well as their
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4 171 spouses when possible, and included assessments of social,
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6 172 economic, and health circumstances of community-residents.
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9 173 The national baseline survey was conducted between June
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11 174 2011 and March 2012 and samples were chosen through
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13 175 multistage probability sampling. After excluding empty or
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15 176 non-resident dwellings, final interviews were conducted on
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17 177 17,708 respondents from 10,257 households, which completed
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19 178 at least one module of the survey beyond the cover screening
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21 179 for age eligibility. CHARLS respondents were followed every
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23 180 2 years, using a face-to-face computer-assisted personal
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25 181 interview (CAPI) ^[14]. SHS mainly affects married women in
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27 182 China. Though unmarried or cohabiting women can possibly
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29 183 be affected by household SHS, this kind of influence
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31 184 remains scarce. At baseline, there were 3381 married women
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33 185 who never smoked cigarettes and lived with spouses who had
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35 186 either smoked cigarettes in the past or smoked at the time
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37 187 of interview. Data for each variable was therefore
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39 188 collected for those respondents. Our final sample was
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41 189 composed of 6875 respondents. Among them, 2802 were
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43 190 interviewed again during the second wave of data collection
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45 191 in 2013, and 2247 were interviewed again during the third
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47 192 wave in 2015. The similar sample selection process was
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4 193 conducted for participants in the second wave in 2013 as a
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6 194 baseline. The final sample consisted of 1799 women who were
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9 195 investigated again in 2015 as participants.
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11 196 **Measures**

12 197 ***Secondhand Smoke***

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17 198 In this study, the exposure to SHS among Chinese women
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19 199 was assessed through several surveys based on the
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21 200 standardized CHARLS questionnaire. Questions about the
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23 201 participant's current marital status, the year they got
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25 202 married, and the year the husband in each household has
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27 203 begun or ceased smoking at home were asked.
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32 204 The smoking status section contained four questions:
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34 205 "Have you ever chewed tobacco, smoked a pipe, smoked self-
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36 206 rolled cigarettes, or smoked cigarettes/cigars?", "Do you
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38 207 still have the habit or have you totally quit?", "At what
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40 208 age did you totally quit smoking?" and "At what age did you
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42 209 start to smoke on a regular basis?". If the answer to the
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44 210 first question was "yes", they were defined as "current
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46 211 smokers" or "ex-smokers". Our analysis of SHS exposure
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48 212 focused only on never smokers excluding the "current
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50 213 smokers" and "ex-smokers", because of the difficulty to
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52 214 differentiate the negative effects of active smoking on
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4 215 health condition from that of SHS exposure. The length of
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6 216 SHS exposure was calculated and expressed as the total
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9 217 number of years that never-smoking women spent living with
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11 218 their spouses who smoked cigarettes at home.

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13
14 219 Categorical classification of SHS was used because the
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16 220 impact of SHS might be neglected if we only used a
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18
19 221 continuous variable to represent exposure. Similarly
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21 222 compared with continuous variables categorical variables
22
23
24 223 have greater public health significance. Based on the
25
26 224 constructed SHS exposure variable, participants were
27
28
29 225 classified into four different groups: Never or being
30
31 226 exposed to SHS for less than 25 years, more than 25 years
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34 227 and less than 30 years, more than 30 years and less than
35
36 228 40 years and over 40 years. The cut-off boundaries of SHS
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38
39 229 exposure were decided to realize the relatively balanced
40
41 230 population distribution frequency among different levels
42
43
44 231 of exposure year.

45 46 47 48 232 ***Cognitive function***

49
50 233 The cognitive function of the respondents in CHARLS
51
52 234 questionnaires was measured through a question-and-answer
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55 235 interview instrument, and the respondents were followed
56
57
58 236 every two years using a face-to-face, computer-aided
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4 237 personal interview (CAPI). The various sections of the questionnaire could
5
6 238 assess cognitive subdomains including visuospatial ability, orientation and attention,
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9 239 and episodic memory. Figure drawing was tested by asking the participants to
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11
12 240 reproduce a picture of two overlapped pentagons in CHARLS questionnaires^[18]. It was
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15 241 used to measure a person's ability to identify visual and spatial relationships among
16
17 242 objects. The Telephone Interview of Cognitive Status (TICS)
18
19 243 was a screening test, including serial subtractions of 7
20
21
22 244 from 100 (up to 5 times), date (month, day, and year and
23
24
25 245 season), and the day of the week. In order to assess orientation and
26
27 246 attention function, the number of correct answers to the above questions in TICS was
28
29
30 247 scored and summed up (range 0 to 10). Participants who successfully completed the
31
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33 248 task received a score of 1, and those who failed received 0^[19].

34
35 249 In addition, the word recall test consisted of 2
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38 250 components, immediate recall and delayed recall, and
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40
41 251 evaluated episodic memory. Participants were required to
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43
44 252 repeat 10 Chinese nouns just read to them, and then after
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46
47 253 20 questions concerning Center for Epidemiologic Studies
48
49 254 Depression Scale (CES-D, approximately 4 to 10 minutes)
50
51 255 they were again asked to recall as many of the original
52
53
54 256 words as possible. The item was coded as 1 if recalled by
55
56
57 257 the respondent, and as 0 if not. Scores for immediate and
58
59 258 delayed recall both varied from 0 to 10. An evaluated
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259 episodic memory score was calculated using the mean of
260 scores in immediate and delayed word recall (range 0 to 10)
261 [19].

262 The overall cognition scores were the sum of the three
263 different domains (range 0 to 21).

264 ***Control variables***

265 Given that cognitive function may vary across
266 demographic and socioeconomic status, we thus included age,
267 urban/rural residence, education, annual household
268 expenditures, chronic diseases and depressive symptoms as
269 control variables. Education was categorized into 3 groups:
270 "illiterate", "primary education" and "secondary education
271 or above". Arterial hypertension and diabetes mellitus are
272 separately strong independent risk factors for the
273 development of cognitive impairment and dementia^[20] ^[21].
274 Thus, the baseline chronic disease of hypertension and
275 diabetes were classified as three types based on self-
276 reported conditions on whether the participants were being
277 treated: having hypertension/diabetes with treatment,
278 having hypertension/diabetes without treatment and not
279 having hypertension/diabetes. The measure of depressive
280 symptoms was based on the 10-item version of the CES-D

281 short form, and each of the 4-option response to the item
282 was scored ranging from 0 to 3. The total score is the sum
283 of points for all 10 items, and a score of 10 or higher
284 suggests the presence of depressive symptoms ^[6].

285

286 ***Patient and Public Involvement***

287 No patient involved.

288 **Analysis**

289 All analyses were conducted with STATA, version 14.0
290 (Stata, College Station, TX, USA). The lagged dependent-
291 variable (LDV) regression models with ordinary least
292 squares estimation were used during analysis. LDV models
293 were superior for analyzing the effects of predictor
294 variables on an outcome with 2-wave panel data while
295 controlling for the influence of time-invariant
296 variables^[22]. It adjusted for baseline cognitive conditions
297 for all participants, therefore provided more robust
298 estimates of the effects of independent variables. After
299 pooling the three sets of panel data into one through using
300 the "year" dummy variable to differentiate between a change
301 in 2 years or in 4 years, we have 6875 respondents who have
302 complete data on all variables. The overall cognitive

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4 303 scores, episodic memory scores, visuospatial ability scores
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6 304 and orientation and attention scores were 4 separate
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9 305 outcome variables. The different groups of SHS exposure
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11 306 years were the predictor variable, and other independent
12
13 307 variables included all demographic and socioeconomic
14
15 308 characteristics. Prior to fitting the regression models,
16
17 309 descriptive analyses were conducted to estimate the mean
18
19 310 and standard deviations for continuous data and frequencies
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21 311 and percentages for categorical data.
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313 **Results**

314 Table 1 provides a descriptive summary of all the
315 variables for participants from each panel of three
316 different waves: 2011-2013, 2011-2015 and 2013-2015. High
317 prevalence of SHS exposure between 30 to 40 years was seen
318 in different panels, accounting for 32.51%, 35.18% and
319 42.69% respectively.

320 The participants were over 45 years old, with the mean
321 age of 56, 56 and 58 years old, respectively in those waves.
322 Participants were more likely to live in a rural area, have
323 a lower education background and not to have hypertension
324 or diabetes diagnoses at baseline. In addition, our results
325 indicated that the mean baseline cognition scores were

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4 326 higher than cognition scores after 2 or 4 years. The mean
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6 327 scores of CES-D suggested that the prevalence of depression
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9 328 among Chinese middle-aged and old-aged women increased in
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11 329 those years. Other socio-demographic characteristics of the
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14 330 respondents are shown in Table 1

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17 331 Results from the regression models for the
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19 332 relationship between SHS exposure and each domain of the
20
21
22 333 cognitive function and overall cognition scores are
23
24 334 reported in Table 2 and Table 3. Scores of episodic
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26
27 335 memory, orientation and attention and visuospatial among
28
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30 336 respondents at baseline were strong predictors of their
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33 337 corresponding cognitive function measures after 2 or 4
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35 338 years. Based on the analysis adjusted for age, annual
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38 339 household expenditure, education, baseline cognitive
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40 340 function and another chronic health status, we found that
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43 341 only being exposed to SHS for more than 40 years was
44
45 342 significantly associated with a decline in visuospatial
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48 343 abilities, episodic memory and overall cognition scores
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51 344 for all respondents. Compared with respondents who were
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53 345 not exposed to SHS or exposed to it for less than 25
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56 346 years, those who have been exposed to SHS for more than
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58 347 40 years was associated with a 0.04-point decline in
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4 348 visuospatial abilities (95%CI, -0.08 to -0.01 P <0.1), a
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6 349 0.16-point decline in episodic memory (95%CI, -0.31 to -
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8 350 0.01 P <0.05), and a 0.33-point decline in overall
9
10
11 351 cognition function (95%CI, -0.66 to -0.01 P <0.01). In
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14 352 addition, age was also negatively associated with
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17 353 cognitive function. Each one-year older was associated
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19 354 with 0.01-point, 0.01-point, 0.03-point, and 0.05-point
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21
22 355 decrease in visuospatial (95%CI, -0.01 to -0.00 P <0.01),
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24 356 orientation (95%CI, -0.03 to -0.01 P <0.01), memory
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26
27 357 (95%CI, -0.31 to -0.01 P <0.05) and overall cognition
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30 358 scores (95%CI, -0.66 to -0.01 P <0.01), respectively.
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33 359 High education level was associated with better cognitive
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35 360 performance, especially in orientation and attention. In
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38 361 addition, a one-point increase in CESD scores was
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41 362 associated with 0.02-point decrease in scores of
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43 363 orientation and attention (95%CI, -0.03 to 0.00 P <0.05),
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45 364 showing that respondents with depressive symptoms were
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48 365 more likely to demonstrate a cognitive decline in
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51 366 specific functions.

367 **Discussion**

368 Results from this longitudinal study with a large,
369 representative sample of middle-aged and older women in

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4 370 China indicated that exposure to SHS for over 40 years was
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6 371 significantly associated with declining performance of
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9 372 global cognition and cognitive subdomains. It is the first
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11 373 examination of cognitive subdomains concerning household
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14 374 SHS exposure using a 4-year longitudinal data in China. The
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17 375 inferior performance of SHS on visuospatial abilities,
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19 376 episodic memory and orientation and attention abilities are
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22 377 novel because these domains were not specifically evaluated
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25 378 in earlier studies among middle-aged and older women who
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27 379 never smoke. This study builds on previous findings that
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30 380 SHS was associated with poor cognitive performance,
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32 381 especially in children, adolescents and adults ^[18]. We found
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35 382 that having a high educational level, living in an urban
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38 383 area and having better baseline cognitive function would
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40 384 improve their cognitive performance. The episodic memory
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43 385 score of participants with diabetes at baseline decreased
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46 386 by 0.172 points compared with those without diabetes, which
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48 387 is similar to previous findings^[9].

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50 388 Moreover, our results showed that compared with women
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53 389 who have never been exposed to SHS or have been exposed for
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56 390 less than 20 years, those who have been exposed to SHS for
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59 391 more than 40 years have a significant decline in
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4 392 visuospatial function (0.04-point), episodic memory (0,16-
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6 393 point) and overall cognitive scores (0.33-point). These
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9 394 findings were similar in magnitude to prior research on the
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11 395 relationship between SHS and cognitive function ^[14]. Moheet
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14 396 and colleagues (2015) conducted a cross-sectional study in
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17 397 the North East of England to explore the impact of diabetes
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19 398 on cognitive function and brain structure (N=150). Research
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22 399 suggested that compared with non-exposed people,
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25 400 participants who had no history of smoking and being
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27 401 averagely exposed to SHS for around 6 years showed
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30 402 significantly reduced performance in processing speed (i.e.
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33 403 how quickly one can process information and perform tasks)
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35 404 and executive function (i.e. the ability to organize memory,
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38 405 cognitive flexibility, and problem-solving ability) ^[22].
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40 406 Another longitudinal ageing study in China (N=4809, ages
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43 407 ≥ 50) found that never smokers exposed to the highest levels
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45 408 of SHS (salivary cotinine concentrations 0.8-13.5 ng/ml)
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48 409 were more likely to be cognitively impaired (odds ratio
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51 410 =1.70) than those exposed to little or no SHS ^[18].

52
53 411 Attention referred to the ability to concentrate and
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56 412 focus on specific stimuli slightly declined in later life
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58 413 ^[13]. Orientation was one's ability to identify the exact

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4 414 date, month, day and season of the year^[23]. Our results
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6 415 suggested that for each one-year increase in age, there
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9 416 were additional 0.01-point, 0.02-point, 0.04-point and
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11 417 0.06-point decline in visuospatial, orientation, memory and
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13
14 418 overall cognition scores, respectively. SHS seems to be
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16
17 419 more strongly associated with cognitive decline than ageing,
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19 420 since the magnitude of significant coefficient between
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22 421 SHS and cognitive decline was almost four times the one in
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24
25 422 ageing. However, the relationship between SHS and
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27 423 orientation and attention ability was not observed. This
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30 424 may since the size of the sample is relatively small, plus
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33 425 the period of cohort study after controlling for all
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35 426 demographic and socioeconomic confounders is relatively
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38 427 short.

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40 428 Visuospatial abilities involve the ability to understand
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43 429 space in two and three dimensions. In our study, an inversed
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46 430 relationship between SHS exposure and visuospatial
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49 431 abilities among middle-aged and older adults was observed,
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51 432 showing a 0.04-point decline in their visuospatial scores.
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54 433 Such an inversed relationship between SHS exposure and
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57 434 visuospatial reasoning skills was also reported among
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59 435 American children (N=5683; ages 6-16), showing that years
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4 436 of SHS exposure was significantly associated with lower
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6 437 scores for reading, math, and visuospatial skills, after
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9 438 adjusting for covariates ^[15]. As one of the most common
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11 439 cognitive complaints among elders, episodic memory refers
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14 440 to personally experienced events which could be measured
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17 441 by stories, word lists or figures. Previous research has
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19 442 indicated that the onset of memory decline may vary among
20
21 443 different memory types, with episodic memory decline
22
23 444 possibly being lifelong ^[24]. Our study could not explore
24
25 445 the onset age of memory decline without doing regression
26
27 446 among different age groups. The significant coefficient may
28
29 447 indicate memory decline associated with SHS exposure.

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35 448 The inconsistent conclusions between our studies and
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37 449 prior ones may be due to the relatively simplified version
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39 450 of the cognition test procedure in CHARLS questionnaires
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41 451 compared with the Montreal Cognitive Assessment (MoCA) ^[14]
42
43 452 and Mini-Mental State Examination (MMSE) ^[25]. Some studies
44
45 453 also used clinical or magnetic resonance imaging (MRI)
46
47 454 evidence of neurologic damage to detect cognitive
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49 455 impairment. The MoCA functions best as a screening test,
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51 456 having exhibited excellent sensitivity in identifying MCI
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53 457 and AD (Alzheimer's disease) at 90% and 100%, respectively
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4 458 [26].

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6 459 The most popular hypothesis about the mechanisms
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9 460 underlying the links between SHS exposure and more
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11 461 unsatisfactory cognitive performance lies in the notion
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14 462 that the carbon monoxide (CO) in tobacco smoke may
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17 463 interfere with the oxygen being delivered to the brain via
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19 464 the blood. However, the reasons behind the different
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22 465 effect on various domains of brain function are far from
23
24
25 466 clear. One possible explanation derives from research on
26
27 467 laboratory animals. Exposing animals to varying degrees of
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30 468 toxic mixtures of chemicals found in tobacco smoke may
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33 469 lead to reduced neuronal mass in specific regions of the
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35 470 brain associated with learning and memory. Since the
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38 471 hippocampal region of the brain is known to be involved
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40 472 in the mediation of memory [27] and learning, further
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43 473 research should be conducted in other regions dominating
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45
46 474 visuospatial and orientation ability. Another possible
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48 475 mechanism is that prolonged exposure to SHS may be a
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50
51 476 significant risk factor for cardiovascular disease
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53 477 (CVD) [28], which may therefore lead to a range of health
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56 478 and cognitive problems in later life. In the future, a
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59 479 longitudinal design may elucidate any associations by
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4 480 observing long-term exposure to SHS and the incidence of
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6 481 CVD, and whether this CVD may mediate or interact with SHS
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9 482 exposure to impact cognitive function.

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11 483 Several limitations need to be considered when interpreting
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13
14 484 this study and designing future studies. Firstly, exposure
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16
17 485 to SHS was evaluated based on self-report measures. This
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19
20 486 might be subject to recall bias and lead to over-or-
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22 487 underestimation of exposure [29]. Therefore, further studies
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25 488 could include more biological assays, for example, cotinine
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27 489 residue levels or nicotine residue in saliva or hair
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30 490 samples [30]. Previous research using serum cotinine as a
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33 491 biomarker of exposure to SHS found that higher levels of
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36 492 serum cotinine were associated with significantly worse
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38 493 performance in reading, mathematics, and visual and spatial
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40 494 abilities in children and adolescents [8]. However, no
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43 495 studies have used a combination of biomarker and self-
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46 496 reporting yet [31]. Some validated biomarkers could be used
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49 497 as proxies for AD neuropathological changes, such as
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51 498 cerebrospinal fluid (CSF) amyloid-beta (A β)42
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53 499 concentrations or A β 42/ A β 40 ratio and amyloid load on
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56 500 positron emission tomography (PET) scans. These biomarkers
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59 501 could provide more reliable measures of cognitive
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4 502 impairment^[32]. Secondly, it may be impossible to control
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6 503 for all potentially confounding variables. After adjusting
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9 504 for age, household expenditure, education, area, chronic
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11 505 health condition and depressive symptoms, some other
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14 506 demographic or socioeconomic confounders may still have
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17 507 been neglected. However, this did not appear to affect the
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19 508 magnitude of the association between SHS exposure and
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22 509 cognition ^[14]. Besides, the analyses only contained
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25 510 household SHS exposure, which precluded the analyses of the
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27 511 influence of environmental smoke inhalation on smoking
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29
30 512 proclivity. Whether exposure to household SHS can hasten
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32
33 513 the onset of cognitive impairment for older Chinese women
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35 514 could be further proved by running regression models in
36
37
38 515 different age groups.

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42
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46
47
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49 50 520 **Conflict of Interest**

51
52
53 521 The authors have no conflicts of interest to declare.

54 55 522 **Author's Contribution**

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4 523 Anying Bai wrote and participated in all aspects of this research, including the field
5
6 524 investigation. Dr Yangmu Huang reviewed and supervised this research. Yinzi Jin
7
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9 525 participated in the statistical analysis of this work and reviewed the final article.
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12 526 **Data sharing statement**

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14 527 CHARLS data is available to the public online: <http://charls.pku.edu.cn>
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16

17 528 **Funding Resources**

18
19 529 This is a self-funded research.
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23 531 **Reference**

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Table 1. Characteristics of the Participants from 3 waves of CHARLS, 2011-2013-2015

Variable	2011-2013 (N=2802)		2011-2015 (N=2274)		2013-2015 (N=1799)	
	Count	Frequency	Count	Frequency	Count	Frequency
Area						
Urban	981	35.01%	730	32.10%	556	30.91%
Rural	1821	64.99%	1544	67.90%	1243	69.09%
SHS						
Less than 25 years	759	27.09%	531	23.35%	262	14.56%
More than 25 years and less than 30 years	634	22.63%	573	25.20%	385	21.40%
More than 30 years and less than 40 years	911	32.51%	800	35.18%	768	42.69%
More than 40 years	498	17.77%	370	16.27%	384	21.35%
Education						
Illiterate	1552	55.39%	1309	57.56%	1004	55.81%
Primary education	512	18.27%	414	18.21%	336	18.68%
Secondary or above	738	26.34%	551	24.23%	459	25.51%
Hypertension						
No hypertension	2124	75.80%	1720	75.64%	1365	75.88%
Hypertension with treatment	522	18.63%	1720	75.64%	358	19.90%
Hypertension without treatment	156	5.57%	130	5.72%	76	4.22%
Diabetes						
No Diabetes in baseline	2643	94.33%	2140	94.11%	1704	94.72%

Have Diabetes with treatment	143	5.10%	120	5.28%	86	4.78%
Have Diabetes without treatment	16	0.57%	14	0.62%	9	0.50%
	Count	Mean (SD)	Count	Mean (SD)	Count	Mean (SD)
Age	2802	55.84 (8.22)	2274	56.19 (7.75)	1799	57.90 (7.43)
Annual Household Expenditure, yuan ^a	2802	13786.99 (14197.29)	2274	13060.14 (13639.33)	1799	16632.84 (18568.24)
Visuospatial ability ^b	2802	0.51 (0.50)	2274	0.48 (0.50)	1799	0.49 (0.50)
Orientation and attention ^c	2802	5.87 (3.29)	2274	5.84 (3.19)	1799	5.97 (3.14)
Memory Scores ^d	2802	3.33 (1.96)	2274	3.04 (1.93)	1799	3.15 (1.91)
Baseline Visuospatial ability	2802	0.57 (0.50)	2274	0.55 (0.50)	1799	0.54 (0.50)
Baseline Orientation and attention	2802	6.39 (2.92)	2274	6.25 (2.90)	1799	6.16 (3.00)
Baseline Memory Scores	2802	3.27 (1.98)	2274	3.23 (1.92)	1799	3.50 (1.78)
Baseline CES-D Score ^e	2802	12.09 (5.38)	2274	12.13 (5.45)	1799	10.90 (5.14)

Abbreviation: SHS, secondhand smoke.

a 1 US dollar = 6.3 yuan.

b The score range for visuospatial ability was 0-1.

c The score range for orientation and attention was 0-10. Higher scores indicate better mental status.

d The score range for episodic memory was 0-10. Higher scores indicate better memory function.

e A score of 10 or greater indicated the presence of depressive symptoms.

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Table 2. Adjusted Multivariable linear regression analysis of the relationship between smoking exposure and Visuospatial function and Orientation and Attention among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Visuospatial Function			Orientation and Attention		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.01 ^a	-0.01, -0.00	-6.73	-0.02 ^a	-0.03, -0.01	-4.34
Expenditure	0.00	0.00, 0.00	0.01	0.00 ^a	0.00, 0.00	0.77
SHS Exposure^d						
25 to <30 years	-0.01	-0.04, 0.02	-0.72	0.05	-0.12, 0.21	0.56
≥30 to <40 years	-0.02	-0.05, 0.02	-0.95	-0.03	-0.20, 0.13	-0.38
≥ 40 years	-0.04 ^c	-0.08, 0.01	-1.67	-0.15	-0.38, 0.09	-1.24
Baseline Visuospatial Function	0.23 ^a	0.21, 0.26	17.93			
Baseline Orientation and Attention				0.55 ^a	0.53, 0.57	44.86

Urban^e	0.06 ^a	0.04, 0.09	5.27	0.38 ^a	0.25, 0.51	5.72
Education^f						
Primary	0.23 ^a	0.20, 0.26	14.00	1.11 ^a	0.94, 1.27	12.91
Secondary or Above	0.29 ^a	0.26, 0.32	18.51	1.18 ^a	1.01, 1.36	13.44
Hypertension^g						
With Treatment	-0.03	-0.09, 0.02	-1.20	0.06	-0.24, 0.35	-0.38
Without Treatment	-0.02	-0.06, 0.03	-0.69	0.06	-0.11, 0.24	0.04
Missing Group	-0.05 ^c	-0.12, 0.01	-1.67	0.06	-0.19, 0.30	-0.01
Diabetes^h						
With Treatment	0.02	-0.03, 0.07	0.90	0.25 ^c	-0.03, 0.52	-1.77
Without Treatment	0.03	-0.04, 0.09	0.82	0.21	-0.06, 0.48	-0.23
Missing Group	0.07	-0.08, 0.21	0.88	0.50	-0.22, 1.23	0.67
Baseline CES-D Score	-0.00 ^c	-0.00, 0.00	-1.71	-0.02 ^b	-0.03, -0.00	-2.57
year = 2	-0.02	-0.04, 0.01	-1.58	0.09	-0.05, 0.22	1.29

Abbreviations: CI, confidence interval; SHS, secondhand smoke.

a. $p < 0.01$

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5 b. $p < 0.05$

6 c. $p < 0.1$

7 d. Referent: No SHS exposure or Less than 25 years.

8 e. Expenditure is expressed as the natural log of the annual household expenditure

9 f. Referent: Illiterate

10 g. Referent: Without hypertension

11 h. Referent: Without diabetes

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14 I. This model adjusted for age, expenditure, living area, education, baseline hypertension, diabetes, depression status and baseline cognitive function.

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Table 3. Adjusted Multivariable linear regression analysis of the relationship between smoking exposure and Episodic memory and Overall cognitive function among older Chinese women (N = 6875), 2011-2013-2015

VARIABLES	Episodic Memory			Overall Cognition		
	β coefficient	95%CI	t	β coefficient	95%CI	t
Age	-0.04 ^a	-0.05, -0.03	-11.37	-0.06 ^a	-0.07, -0.04	-7.87
Expenditure	0.00	0.00, 0.00	1.30	0.00 ^a	0.00, 0.00	0.32
SHS Exposure^d						
25 to <30 years	-0.04	-0.16, 0.08	-0.67	-0.01	-0.25, 0.25	-0.01
≥30 to <40 years	0.02	-0.09, 0.13	0.36	-0.05	-0.29, 0.19	-0.41
≥ 40 years	-0.16 ^b	-0.31, -0.01	-2.06	-0.33 ^a	-0.66, 0.01	-1.93
Baseline Episodic Memory	0.30 ^a	0.28, 0.32	25.22			
Baseline Overall Cognition				0.55 ^a	0.46, 0.83	44.95

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6	Urban^e	0.25 ^a	0.16, 0.34	5.60	0.65 ^a	0.46, 0.83	6.68
7							
8	Education^f						
9	Primary	0.70 ^a	0.58, 0.80	12.42	1.77 ^a	1.53, 2.02	14.28
10							
11	Secondary or Above	0.97 ^a	0.86, 1.08	17.29	2.00 ^a	1.74, 2.26	15.24
12							
13	Hypertension^g						
14	With Treatment	0.04	-0.16, 0.23	0.35	0.13	-0.29, 0.56	0.62
15							
16	Without Treatment	0.06	-0.06, 0.17	0.95	0.12	-0.14, 0.38	0.93
17							
18	Missing Group	0.07	-0.12, 0.25	0.70	0.10	-0.27, 0.47	0.52
19							
20	Diabetes^h						
21	With Treatment	-0.20 ^b	-0.38, 0.02	-2.20	-0.04	-0.43, 0.36	0.62
22							
23	Without Treatment	-0.07	-0.25, 0.11	-0.77	0.08	-0.30, 0.47	0.43
24							
25	Missing Group	0.32	-0.16, 0.80	1.30	0.87	-0.11, 1.84	1.75
26							
27	Baseline CES-D Score	-0.01 ^b	-0.01, 0.00	-1.59	-0.01	-0.03, 0.00	-2.57
28							
29	year = 2	-0.24	-0.33, -0.15	-5.21	-0.17	-0.37, 0.03	-1.70
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Constant	0.63	0.53, 0.74	11.54	6.48 ^a	5.59, 7.37	14.28
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Abbreviations: CI, confidence interval; SHS, secondhand smoke.

a. $p < 0.01$

b. $p < 0.05$

c. $p < 0.1$

d. Referent: No SHS exposure or Less than 25 years.

e. Expenditure is expressed as the natural log of the annual household expenditure

f. Referent: Illiterate

g. Referent: Without hypertension

h. Referent: Without diabetes

I. This model adjusted for age, expenditure, living area, education, baseline hypertension, diabetes, depression status and baseline cognitive function.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
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19	Generalisability	21	Discuss the generalisability (external validity) of the study results	12
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21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17
23				
24				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.