



Prospective investigation of type 2 diabetes in relation to lung cancer risk among 133,024 Chinese adults

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004875
Article Type:	Research
Date Submitted by the Author:	17-Jan-2014
Complete List of Authors:	Yang, Wan-Shui; Jiujiang University, Social Science and Public Health Yang, Yang; Shanghai Cancer Institute, Yang, Gong; Vanderbilt School of Medicine, Department of Medicine Chow, Wong-Ho; University of Texas MD Anderson Cancer Center, Li, Honglan; Shanghai Cancer Institute, Department of Epidemiology Gao, Yu-Tang; Shanghai Cancer Institute, Department of Epidemiology Ji, Butian; National Institutes of Health, 3Division of Cancer Epidemiology and Genetics Rothman, Nat; National Cancer Institute, Shu, Xiao-Ou; Vanderbilt School of Medicine, Department of Medicine Zheng, Wei; Vanderbilt School of Medicine, Department of Medicine Xiang, Yong-bing; Shanghai Cancer Institute, Department of Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Oncology, Diabetes and endocrinology
Keywords:	EPIDEMIOLOGY, ONCOLOGY, Epidemiology < ONCOLOGY, Adult oncology < ONCOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Prospective investigation of type 2 diabetes in relation to lung cancer risk among 133,024**

2 **Chinese adults**

3 Wan-Shui Yang^{1,2,3}, Yang Yang^{1,2}, Gong Yang⁴, Wong-Ho Chow⁵, Hong-Lan Li^{1,2}, Yu-Tang Gao²,
4 Bu-Tian Ji⁶, Nat Rothman⁶, Wei Zheng⁵, Xiao-Ou Shu⁵, Yong-Bing Xiang^{1,2}

5 **Author affiliations:**

6 1. State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital,
7 Shanghai Jiaotong University School of Medicine, Shanghai, China.

8 2. Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong
9 University School of Medicine, Shanghai, China.

10 3. Department of Social Science and Public Health, School of Basic Medical Science, Jiujiang
11 University, Jiujiang, China.

12 4. Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center,
13 Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, USA.

14 5. Division of Cancer Prevention and Population Sciences, Department of Epidemiology, University
15 of Texas MD Anderson Cancer Center, Houston, Texas, USA.

16 6. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, USA.

17 **Corresponding author:** Prof. Yong-Bing Xiang, Shanghai Cancer Institute, Renji Hospital, Shanghai
18 Jiaotong University School of Medicine, No. 25, Lane 2200, Xie Tu Road, Shanghai 200032, P. R.
19 China, Telephone: 86-21-64437002, Fax: 86-21-64046550, E-mail: ybxiang@shsci.org

20 **Word count:** Text: 2572 words; Abstract: 244 words

21 **Tables: 3 ; Figures: 0**

22 **Keywords:** type 2 diabetes; lung cancer; cohort study; Shanghai

1
2
3 23 **List of abbreviations:** BMI, body mass index ; CI, confidence interval; MET, metabolic equivalents;
4
5 24 HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin-like growth factor; PA, physical
6
7 25 activity; RR, relative risk; SMHS, Shanghai Men’s Health Study; SWHS, Shanghai Women’s Health
8
9
10 26 Study; T2D, type 2 diabetes; WHR, waist-to-hip ratio
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Abstract

Objectives: Observational studies of type 2 diabetes (T2D) and lung cancer risk is limited and controversial. We thus examined the association between T2D and risk of incident lung cancer using a cohort design and a meta-analytic approach.

Setting: We conducted two prospective population-based cohort studies (Shanghai Men's Health Study and Shanghai Women's Health Study) in China. Cox proportional hazards regression models with T2D as a time-varying exposure were modeled to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Participants: The study population included 61,491 male participants aged 40-74y from Shanghai Men's Health Study and 74,941 female participants aged 40-70y from Shanghai Women's Health Study.

Outcome measure: Lung cancer cases were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics, and were further verified through home visits and review of medical charts by clinical and/or pathological experts.

Results: During follow-up through 2010, 1017 incident lung cancer cases (492 for men and 525 for women) were identified among 59,910 men and 73,114 women. After adjustments for smoking, alcohol drinking, body mass index, physical activity, and other potential confounders, T2D is not associated with the lung cancer risk either in men (HR=0.87, 95%CI: 0.62-1.21) or in women (HR=0.92, 95%CI: 0.69-1.24). Analyses after excluding lung cancer cases occurred within the first 3 years after diabetes onset and among never smokers yielded similar results.

Conclusions: There is little evidence that preexisting T2D may influence the incidence of lung cancer.

1
2
3 50 **Strengths and limitations of this study**
4
5

- 6 51 ● We showed a null association between type 2 diabetes and risk of lung cancer in two
7
8 52 population-based prospective cohorts with large sample size and long term follow-up.
9
10
11 53 ● This null association was remained after excluding lung cancer cases occurred within the first 3
12
13 54 years after diabetes onset and among never smokers.
14
15
16
17 55 ● However, using self-reported diabetes as exposure, and the lack of pharmacologic data on
18
19 56 diabetes treatments including hypoglycemic agents use and degree of glucose control do not allow
20
21 57 firm conclusions.
22
23
24
25 58

59 Introduction

60 Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer-related
61 death globally and in China¹. The prevalence of diabetes has increased substantially in China, with
62 the age-standardized rates from 2.4% in 1994² to 9.7% in 2007 to 2008³.

63 Individuals with preexisting type 2 diabetes (T2D) have been shown to be at risk for a number of
64 cancers, including cancers of the liver^{4,5} and pancreas⁶. A link between type 2 diabetes and lung
65 cancer risk has also been suggested, but the evidence is limited and inconsistent. An inverse
66 association was observed in four cohort studies⁷⁻¹⁰, whereas an elevated risk of lung cancer was
67 associated with type 2 diabetes in five other cohort studies, particularly among women¹¹⁻¹⁵. Other
68 studies, including eight cohort¹⁶⁻²³ and two case-control^{24,25} studies, have reported a null association.
69 These discrepancies could be due to a number of factors including insufficient statistical power (small
70 sample size), different study designs and exposure ascertainment, and the lack of adjustments for
71 important covariates such as smoking and body mass index (BMI). In addition, all previous studies
72 only considered a single measurement of diabetes at baseline survey, and diabetes newly identified
73 over follow-up periods were neglected, which may have resulted in some underestimation of the true
74 associations.

75 To further clarify whether type 2 diabetes influence the risk of lung cancer, we assessed the
76 association of type 2 diabetes with the risk of lung cancer by using data from the Shanghai Men's
77 Health Study (SMHS) and the Shanghai Women's Health Study (SWHS), two on-going large
78 population-based, prospective cohorts in urban Shanghai, China.

79 Methods

80 *Study population*

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

81 The study population included 61,491 male participants of the Shanghai Men's Health Study (SMHS)
82 and 74, 941 female participants of the Shanghai Women's Health Study (SWHS). Consent has been
83 obtained from each subject after full explanation of the purpose and nature of all procedures used.
84 Details of the study design, scientific rationale, and baseline characteristics of the subjects have been
85 published previously^{26 27}. Briefly, for the SWHS, female residents of Shanghai aged 40-70 years old
86 were recruited from 1997-2000, with an overall participation rate of 92.7%. For the SMHS, men aged
87 40-74 years old with no history of cancer were recruited in Shanghai from 2002-2006, with an overall
88 participation rate of 74.1%. Participants were interviewed in person using a structured questionnaire to
89 obtain information on demographic characteristics, lifestyle and dietary habits, medical history, family
90 history of cancer, and other exposures. Anthropometric measurements, including current weight,
91 height, and circumferences of the waist and hip were also taken at baseline.
92 In this analysis, we excluded participants who had a previous history of cancer at enrollment (none for
93 men and n=1598 for women), were younger than 20 years old on the day of diabetes diagnosis to
94 reduce potential bias from including patients with type 1 diabetes (n=3 for men and 3 for women),
95 died of cancers of unknown origin or without diagnosis date (n=126 for men and n=114 for women),
96 had missing values for any of the covariates of interest (n=1458 for men and n=109 for women), and
97 was diagnosed with lung cancer before the diagnosis of diabetes (n=1 for men and n=3 for women).
98 After exclusion, a total of 59,910 men and 73,114 women remained in current analysis.

99 ***Diabetes assessment***

100 The procedures for identification of diabetes cases have been described elsewhere⁴. Briefly, a case of
101 type 2 diabetes was considered to be confirmed if a subject reported having been diagnosed with type
102 2 diabetes by physician(s) and met at least one of the following self-reported items: 1) fasting plasma

1
2 103 glucose concentration ≥ 7 mmol/L on two separate occasions, 2) plasma glucose concentration ≥ 11.1
3
4 104 mmol/L at 2 hours for a 75 g oral glucose tolerance test, and 3) use of insulin or other hypoglycemic
5
6
7 105 agents.
8
9

10 106 ***Follow up and outcome ascertainment***
11

12
13 107 The participants were followed up with home visits every 2 to 3 years to update exposure information
14
15 108 and to ascertain new diagnosis of cancers. For the SMHS, the first follow up interview was conducted
16
17 109 from 2004-2008 with a response rate of 97.6%. For the SWHS, the first, second and third follow ups
18
19 110 were conducted from 2000-2002, 2002-2004 and 2004-2007 with corresponding response rates of
20
21 111 99.8%, 98.7% and 96.7%, respectively.
22
23
24
25

26 112 The incident lung cancer cases were defined as a primary tumor with an International Classification of
27
28 113 Diseases (ICD)-9 code 162, and were identified through annual record linkage to the Shanghai Cancer
29
30 114 Registry and Shanghai Municipal Registry of Vital Statistics. All possible cancer cases were verified
31
32 115 through home visits and further review of medical charts by clinical and/or pathological experts.
33
34
35

36 116 Outcome data through December 31, 2010 for both men and women was used for the present analysis.
37
38
39

40 117 ***Statistical analysis***
41

42
43 118 Cox proportional hazards regression models with age as time scale were used to calculate age-adjusted
44
45 119 and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations
46
47 120 of type 2 diabetes with the risk of incident lung cancer. type 2 diabetes (yes/no) was modeled as a
48
49 121 time-varying exposure in the current study, meaning that information on type 2 diabetes reported in
50
51 122 questionnaire n , was used to prospectively categorize participants for the periods between completion
52
53 123 of questionnaires n and $n + 1$, and the risk person-years was allocated to the corresponding groups, the
54
55
56
57
58
59
60

1
2 124 corresponding method was described elsewhere in detail ⁴.
3
4
5 125 Covariates were selected based on their potential to confound or modify the association between type
6
7
8 126 2 diabetes and lung cancer. All covariates were modeled using baseline values. The covariates
9
10
11 127 included in the multivariate-adjusted models were age (<50y, 50-60y, ≥60y), birth cohort (1920s,
12
13 128 1930s, 1940s, 1950s, 1960s), education (≤elementary school, middle school, high school, >high
14
15 129 school), income (low, low to middle, middle to high, high), body mass index (BMI; <18.5, 18.5-24,
16
17 130 24-28, ≥28, according to Chinese standard ²⁸), occupation [housewife (women only), manual, clerical,
18
19 131 and professional], smoking status (never smoking, ever smoking, current smoking, for men), smoking
20
21 132 pack-years (0-10, 10-20, ≥20, for men), ever smoking (yes/no, for women), alcohol drinking(0, 0-1.5,
22
23 133 ≥1.5, drink/day, for men), ever alcohol drinking (yes/no, for women), family history of cancer
24
25 134 (yes/no), total energy intake (kcal/day, quartiles), fruit intake (g/day, quartiles), vegetable intake
26
27 135 (g/day, quartiles), total physical activity [PA; standard metabolic equivalents (METs) as MET-hr/day
28
29 136 in quartiles; 1 MET-hr=15 minutes of moderate intensity activity], history of hepatitis/chronic liver
30
31 137 disease (yes/no), hormone replacement therapy (HRT; yes/no for women only), menopausal status
32
33 138 (pre-/post-menopausal for women only).
34
35
36
37
38
39
40
41 139 We also tested for potential interactions of diabetes with age, income, education, occupation, family
42
43 140 history of lung cancer, alcohol drinking, physical activity, and smoking, by comparing the Cox models
44
45 141 with and without the interaction terms using a likelihood ratio test. In testing of the proportional
46
47 142 hazard assumption by creating interaction of diabetes and a logarithm of time in the model, we found
48
49 143 no violation of proportionality.
50
51
52
53
54 144 To investigate the potential effect for over detection bias (i.e. the increased detection around the time
55
56 145 of type 2 diabetes diagnosis), age-adjusted incidence rates by different time intervals of follow-up

1
2 146 (0–1, 1–3, >3 years) in diabetes cohort and no-diabetes cohort were calculated for lung cancer, which
3
4
5 147 were directly standardized by the entire cohort population.
6

7
8 148 All data analyses were performed with SAS 9.2 (SAS Institute, Cary, NC), and a two-sided *P* value of
9
10 149 0.05 was considered statistically significant if not specified.
11

12 13 14 150 **Results**

15 16 17 151 *Results from the SMHS and SWHS*

18
19
20 152 The distributions of selected baseline characteristics according to type 2 diabetes are shown in Table 1.
21
22 153 In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with
23
24 154 type 2 diabetes at baseline or during follow up periods. Compared to men and women without
25
26 155 diabetes, patients with type 2 diabetes were older and had higher BMI, greater intake of total energy
27
28 156 and vegetable, but less fruit consumption and alcohol drinking at baseline. In SWHS, less than 2.8%
29
30 157 of the women reported ever smoking.
31
32

33
34
35 158 After a median follow-up of 6.3 years for SMHS and 12.2 years for SWHS, 1017 incident cases of
36
37 159 lung cancer (492 men and 525 women) were identified in the two cohorts. For men, the
38
39 160 age-standardized incidence rates (1/100 000 person-years) of lung cancer were 87.48, 20.73, and
40
41 161 161.92 for 0-1, 1-3, ≥ 3 years following the diabetes index date in diabetes cohort, respectively; 112.97,
42
43 162 119.57, and 141.81 for 0-1, 1-3, ≥ 3 years since baseline interview for the cohort without diabetes,
44
45 163 respectively. For women, the age-standardized incidence rates (1/100 000 person-years) were 80.53,
46
47 164 19.81, 72.85 for 0-1, 1-3, ≥ 3 years following the diabetes index date in diabetes cohort, respectively;
48
49 165 and 29.68, 41.43, 69.46 for 0-1, 1-3, ≥ 3 years since baseline interview for non-diabetes cohort,
50
51 166 respectively.
52
53
54
55
56
57
58
59
60

1
2 167 After adjustments for smoking, BMI, alcohol drinking, and other factors, type 2 diabetes was not
3
4 168 associated with the risk of developing lung cancer either in men (HR=0.87, 95%CI: 0.62-1.21) or in
5
6 169 women (HR=0.93, 95%CI: 0.69-1.25) (Table 2). This null association remained when the analysis was
7
8 170 restricted to never smokers (Table 3) or after excluding lung cancer cases diagnosed within the first 3
9
10 171 years after diabetes diagnosis (Table 2). Results from subgroup analysis by waist to hip ratio, waist
11
12 172 circumference, smoking, and menopausal status (women) did not appreciably alter the main results
13
14 173 (Table 3). In addition, we did not observe effect modification by age, income, education, occupation,
15
16 174 family history of lung cancer, alcohol drinking, or physical activity (data not shown).
17
18
19
20
21
22

23 175 **Discussion**

24
25
26 176 No observational study, to our knowledge, has investigated lung cancer risk in relation to type 2
27
28 177 diabetes in mainland China to date. Findings from our population-based cohort study suggested that
29
30 178 type 2 diabetes is not associated with the risk of incident lung cancer among Chinese adults, and were
31
32 179 further confirmed by a recent meta-analysis²⁹. This null association remained regardless of age,
33
34 180 income, education, occupation, family history of lung cancer, alcohol drinking, physical activity,
35
36 181 smoking status, menopausal status, and WHR in stratified analysis.
37
38
39
40
41

42 182 Previous epidemiological studies on type 2 diabetes and lung cancer yielded conflicting results,
43
44 183 varying from a positive^{15 30}, null^{16 18-21 23 31-33} to an inverse⁸⁻¹⁰ association. Differing study design,
45
46 184 sample size or follow up time, and covariates adjustments may, in part, explain this inconsistency. A
47
48 185 comparative study⁷ and 3 cohort studies⁸⁻¹⁰ without adjustments for smoking concluded an inverse
49
50 186 association; two cohort studies that reported a positive association have not adjusted for BMI¹⁵ or
51
52 187 smoking³⁰; two studies^{24 25} with a null association used case-control design; three studies have a
53
54 188 limited follow up periods (<5y)^{10 20} or sample size (<10,000)¹⁴. Consistent with most pertinent
55
56
57
58
59
60

189 studies^{16 18-21 23 31-33} and our meta-analysis, we observed a null association between type 2 diabetes
190 and lung cancer risk overall and among nonsmoking participants.

191 Although a null association was found between T2D and lung cancer, previous observational studies
192 have inconsistently shown the increased risk of incident several cancers among individuals with type 2
193 diabetes, including cancers of liver^{4 5} and pancreas⁶. The potential biologic links between diabetes
194 and cancer risk included hyperinsulinemia (either endogenous due to insulin resistance or exogenous
195 due to administered insulin or insulin secretagogues), hyperglycemia, or chronic inflammation³⁴. The
196 hyperinsulinemia may involve in carcinogenesis by its mitogenic effect via the insulin/ insulin-like
197 growth factor (IGF) axis³⁴. On the other hand, hyperglycemia may cause an abnormal energy balance
198 and impair the effect of ascorbic acid on the intracellular metabolism and reduce the effectiveness of
199 the immune system³⁵, which could favor cancer incidence and progression in diabetic patients. In
200 addition, free fatty acids, interleukin-6, monocyte chemoattractant protein, plasminogen activator
201 inhibitor-1, adiponectin, leptin, and tumor necrosis factor- α , which were produced by adipose tissue
202 among T2D related obesity, may play an etiologic role in regulating malignant transformation or
203 cancer progression³⁴.

204 Strengths of our study include the population-based cohort design, large sample size, high response
205 rates of follow ups (over 96% for in-person home visits), and the use of repeated measures of diabetes
206 status. However, several limitations to this study should be noted. As diabetes was from self-reported
207 data and a number of patients with diabetes did not know they had the disease³⁶, the misclassification
208 of type 2 diabetes cannot be ruled out and could be non-differential, thus led to the underestimation of
209 the true association, although previous validation studies^{37 38} indicated that a self-reported history of
210 diabetes could be reasonably accurate and could provide a useful assessment for broad measures of

1
2 211 diabetes in the large-scale observational study. The validity of the self-reported data for measuring
3
4 212 diabetes is also supported by recent meta-analysis showing that summary RR of studies using medical
5
6
7 213 records or diabetes registry as a means of diabetes ascertainment was consistent with the summary RR
8
9
10 214 of studies using self-report data to determine diabetes (data not shown). In addition, the findings from
11
12 215 SWHS would have been affected by over-detection bias, given higher incidence rate of lung cancer in
13
14 216 the first year following the diabetes index date compared to those without diabetes regardless of
15
16
17 217 different time intervals of follow-up. However, the results were unchanged in the analysis after
18
19
20 218 excluding lung cancer cases occurred within the first 3 years after diabetes onset. Moreover, this
21
22 219 potential increased ascertainment in diabetics is unlikely to occur in SMHS because of the lower
23
24
25 220 incidence rate of lung cancer in the diabetic cohort within the first year after the diabetes diagnosis.
26
27 221 Other limitations to the study include the lack of pharmacologic data on diabetes treatments, including
28
29
30 222 hypoglycemic agents use and degree of glucose control.
31
32
33 223 In summary, our cohort study indicated that type 2 diabetes is not associated with lung cancer risk.
34
35 224 Future research to find other modifiable risk factors for lung cancer should be warranted.
36
37
38 225
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 226 **Acknowledgements** We would like to thank the participants of the Shanghai Men's Health Study and
4
5 227 the Shanghai Women's Health Study for the invaluable contribution to this work.

6
7 228 **Contributions** YBX contributed to the conception and design of the study; YBX, HLL and YTG
8
9 229 acquired data; WSY, YY and YBX performed the statistical analysis and the interpretation of results;
10
11 230 WSY wrote the first draft; All authors contributed to the critical review of the manuscript and
12
13 231 approved the final manuscript; The corresponding author (YBX) had full access to all of the data and
14
15 232 the final responsibility for the decision to submit for publication.

16
17
18 233 **Funding** This work was supported by the fund of Key Discipline and Specialty Foundation of
19
20 234 Shanghai Municipal Commission of Health and Family Planning, and grants from US National
21
22 235 Institutes of Health (R37 CA070867 and R01 CA82729).

23
24 236 **Competing interests** None. The funding sponsor had no role in the study design, data collection,
25
26 237 statistical analysis and result interpretation, as well as in the writing of the report and the decision to
27
28 238 submit for publication. The corresponding author had full access to all data in the study and final
29
30 239 responsibility for the decision to submit for publication.

31
32 240 **Study approval** Institutional review board.

33
34 241 **Ethics approval** IRBs of Vanderbilt University (USA) and Shanghai Cancer Institute (Shanghai,
35
36 242 China).

37
38
39
40
41
42
43
44
45
46 243
47
48
49
50
51
52
53
54
55
56
57
58
59
60

244 **Reference**

- 245 1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;**61**(2):69-90.
- 246 2. Pan XR, Yang WY, Li GW, et al. Prevalence of diabetes and its risk factors in China, 1994. National
247 Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997;**20**(11):1664-9.
- 248 3. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med*
249 2010;**362**(12):1090-101.
- 250 4. Yang WS, Shu XO, Gao J, et al. Prospective evaluation of type 2 diabetes mellitus on the risk of
251 primary liver cancer in Chinese men and women. *Ann Oncol* 2013;**24**(6):1679-85.
- 252 5. Yang WS, Va P, Bray F, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma
253 occurrence and prognosis: a meta-analysis of prospective cohort studies. *PLoS One*
254 2011;**6**(12):e27326.
- 255 6. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of
256 cohort studies. *Eur J Cancer* 2011;**47**(13):1928-37.
- 257 7. Armstrong B, Lea AJ, Adelstein AM, et al. Cancer mortality and saccharin consumption in diabetics.
258 *Br J Prev Soc Med* 1976;**30**(3):151-7.
- 259 8. Atchison EA, Gridley G, Carreon JD, et al. Risk of cancer in a large cohort of U.S. veterans with
260 diabetes. *Int J Cancer* 2011;**128**(3):635-43.
- 261 9. Lo SF, Chang SN, Muo CH, et al. Modest increase in risk of specific types of cancer types in type 2
262 diabetes mellitus patients. *Int J Cancer* 2013;**132**(1):182-8.
- 263 10. Ogunleye AA, Ogston SA, Morris AD, et al. A cohort study of the risk of cancer associated with
264 type 2 diabetes. *Br J Cancer* 2009;**101**(7):1199-201.
- 265 11. Emerging Risk Factors C, Seshasai SR, Kaptoge S, et al. Diabetes mellitus, fasting glucose, and

- 1
2 266 risk of cause-specific death. *N Engl J Med* 2011;**364**(9):829-41.
3
4
5 267 12. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese
6
7 268 men and women. *Eur J Cancer Prev* 2007;**16**(1):83-9.
8
9
10 269 13. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and
11
12 270 insulin effects. *Diabetologia* 2012;**55**(4):948-58.
13
14
15 271 14. Luo J, Chlebowski R, Wactawski-Wende J, et al. Diabetes and lung cancer among postmenopausal
16
17 272 women. *Diabetes Care* 2012;**35**(7):1485-91.
18
19
20 273 15. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and
21
22 274 women. *JAMA* 2005;**293**(2):194-202.
23
24
25 275 16. Coughlin SS, Calle EE, Teras LR, et al. Diabetes mellitus as a predictor of cancer mortality in a
26
27 276 large cohort of US adults. *Am J Epidemiol* 2004;**159**(12):1160-7.
28
29
30 277 17. Saydah SH, Loria CM, Eberhardt MS, et al. Abnormal glucose tolerance and the risk of cancer
31
32 278 death in the United States. *Am J Epidemiol* 2003;**157**(12):1092-100.
33
34
35 279 18. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer: results from a
36
37 280 large-scale population-based cohort study in Japan. *Arch Intern Med* 2006;**166**(17):1871-7.
38
39
40 281 19. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I.
41
42 282 Follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiol*
43
44 283 *Biomarkers Prev* 1995;**4**(8):807-11.
45
46
47 284 20. Hall GC, Roberts CM, Boulis M, et al. Diabetes and the risk of lung cancer. *Diabetes Care*
48
49 285 2005;**28**(3):590-4.
50
51
52 286 21. Khan M, Mori M, Fujino Y, et al. Site-specific cancer risk due to diabetes mellitus history:
53
54 287 evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev*
55
56 288 2006;**7**(2):253-9.
57
58
59
60

- 1
2 289 22. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than
3
4 290 140,000 adults in Austria. *Diabetologia* 2006;**49**(5):945-52.
5
6
7 291 23. Stattin P, Bjor O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes*
8
9 292 *Care* 2007;**30**(3):561-7.
10
11 293 24. Rousseau MC, Parent ME, Pollak MN, et al. Diabetes mellitus and cancer risk in a
12
13 294 population-based case-control study among men from Montreal, Canada. *Int J Cancer*
14
15 295 2006;**118**(8):2105-9.
16
17
18 296 25. O'Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control
19
20 297 study. *J Chronic Dis* 1985;**38**(5):435-41.
21
22
23 298 26. Villegas R, Yang G, Liu D, et al. Validity and reproducibility of the food-frequency questionnaire
24
25 299 used in the Shanghai men's health study. *Br J Nutr* 2007;**97**(5):993-1000.
26
27
28 300 27. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design,
29
30 301 and baseline characteristics. *Am J Epidemiol* 2005;**162**(11):1123-31.
31
32
33 302 28. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive
34
35 303 values of body mass index and waist circumference for risk factors of certain related diseases
36
37 304 in Chinese adults--study on optimal cut-off points of body mass index and waist circumference
38
39 305 in Chinese adults. *Biomed Environ Sci* 2002;**15**(1):83-96.
40
41
42 306 29. Lee JY, Jeon I, Lee JM, et al. Diabetes mellitus as an independent risk factor for lung cancer: a
43
44 307 meta-analysis of observational studies. *Eur J Cancer* 2013;**49**(10):2411-23.
45
46
47 308 30. Chodick G, Heymann AD, Rosenmann L, et al. Diabetes and risk of incident cancer: a large
48
49 309 population-based cohort study in Israel. *Cancer Causes Control* 2010;**21**(6):879-87.
50
51
52 310 31. Ehrlich SF, Quesenberry CP, Jr., Van Den Eeden SK, et al. Patients diagnosed with diabetes are at
53
54 311 increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and
55
56
57
58
59
60

- 1
2 312 pneumonia but not lung cancer. *Diabetes Care* 2010;**33**(1):55-60.
3
4
5 313 32. Wotton CJ, Yeates DG, Goldacre MJ. Cancer in patients admitted to hospital with diabetes mellitus
6
7 314 aged 30 years and over: record linkage studies. *Diabetologia* 2011;**54**(3):527-34.
8
9
10 315 33. Yeh HC, Platz EA, Wang NY, et al. A prospective study of the associations between treated
11
12 316 diabetes and cancer outcomes. *Diabetes Care* 2012;**35**(1):113-8.
13
14
15 317 34. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes*
16
17 318 *Care* 2010;**33**(7):1674-85.
18
19
20 319 35. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. *Endocr Relat Cancer*
21
22 320 2009;**16**(4):1103-23.
23
24
25 321 36. Li R, Lu W, Jiang QW, et al. Increasing prevalence of type 2 diabetes in Chinese adults in
26
27 322 Shanghai. *Diabetes Care* 2012;**35**(5):1028-30.
28
29
30 323 37. Martin LM, Leff M, Calonge N, et al. Validation of self-reported chronic conditions and health
31
32 324 services in a managed care population. *Am J Prev Med* 2000;**18**(3):215-8.
33
34
35 325 38. Wu SC, Li CY, Ke DS. The agreement between self-reporting and clinical diagnosis for selected
36
37 326 medical conditions among the elderly in Taiwan. *Public Health* 2000;**114**(2):137-42.
38
39
40 327
41
42 328
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Type 2 diabetes and lung cancer

Table 1 Characteristics of study participants according to type 2 diabetes status in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)¹

	Men			Women		
	No type 2 diabetes	Type 2 diabetes	<i>P</i> value	No type 2 diabetes	Type 2 diabetes	<i>P</i> value
Number of subjects	55311	4599	-	66,823	6291	-
Mean age at baseline (y)	54.89±9.63	60.48±9.61	<0.001	51.94±8.91	58.51±8.34	<0.001
Education level (%)						
≤Elementary school	6.27	11.33		19.28	43.18	
Middle school	33.51	33.57		37.95	29.27	
High school	36.69	29.53		28.85	18.41	
≥ Prof/Tech/College	23.52	25.57	<0.001	13.92	9.14	<0.001
Income (%) ²						
Low	12.86	9.24		15.58	21.43	
Low-middle	77.45	80.82		38.08	39.88	
Middle-high	8.93	9.26		28.47	24.34	
High	0.76	0.68	<0.001	17.87	14.35	<0.001
Occupation (%)						
Housewife	-	-		0.34	0.64	
Professional	25.79	31.92		29.98	22.78	
Clerical	21.92	22.53		20.81	20.32	
Manual worker	52.29	45.55	<0.001	49.87	56.26	<0.001
BMI kg/m ²	23.64±3.07	24.61±3.04	<0.001	23.82±3.33	26.00±3.76	<0.001
<18.5 (%)	4.49	1.48		3.58	1.30	
18.5-24.0 (%)	50.79	43.23		51.82	29.08	
24.0-28.0 (%)	37.01	41.47		33.83	42.39	
>28 (%)	7.71	13.83	<0.001	10.77	27.23	<0.001

Type 2 diabetes and lung cancer

Table 1 Continued

	Men			Women		
	No type 2 diabetes	Type 2 diabetes	<i>P</i> value	No type 2 diabetes	Type 2 diabetes	<i>P</i> value
Smoking status (%)						
Never smokers	29.69	38.16		97.47	95.25	
Former smokers	10.29	17.33				
Current smokers	60.02	44.51	<0.001	2.59 ³	4.75 ³	<0.001
Physical activity (MET hours/week)	59.56±34.03	61.04±35.83	<0.001	107.00±45.30	102.50±43.31	<0.001
Ever alcohol intake (%)	34.82	29.03	<0.001	2.29	1.87	0.035
Total energy intake (Kcal/day)	8029.80±2029.10	7481.00±1929.50	<0.001	7033.90±1681.10	6845.10±1842.40	<0.001
Fruit intake (g/day)	155.10±125.00	98.58±110.50	<0.001	271.90±178.30	187.90±175.30	<0.001
Vegetable intake (g/day)	341.20±190.10	373.20±218.40	<0.001	295.70±168.70	305.70±188.70	<0.001
Family history of cancer (%)	28.27	30.03	0.011	26.48	26.61	0.821
Post-menopausal (%)	-	-		46.27	76.58	<0.001
HRT use (%)	-	-		2.07	2.10	0.883

¹ Abbreviations: BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-hr=15 minutes of moderate intensity activity); HRT, hormone replacement therapy.

Continuous variables are presented as the mean ± the standard deviation.

² Low: < 10,000 Yuan per family per year for women and <1000 Yuan per person per month for men; Low to middle: 10,000 - 19,999 Yuan per family per year for women and 1000-3000 Yuan per person per month for men; Middle to high: 20,000-29,999 Yuan per family per year for women and 3000-5000 Yuan per person per month for men; High: ≥30,000 Yuan per family per year for women and ≥5000 Yuan per person per month for men.

³ Due to small number of smokers among women, the number of current and former smokers was combined.

Type 2 diabetes and lung cancer

Table 2 Hazard ratios for the association between type 2 diabetes and lung cancer risk in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)

	No type 2 diabetes		Type 2 diabetes		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) ¹
Men					
Entire cohort	450/354,902	1.00(referent)	42/28,825	0.80(0.58-1.10)	0.87(0.62-1.21)
Sensitivity analysis ²	260/354,604	1.00(referent)	28/28,805	0.94(0.64-1.39)	1.10(0.73-1.64)
Women					
Entire cohort	469/801,158	1.00(referent)	56/72,600	0.88(0.66-1.18)	0.93(0.69-1.25)
Sensitivity analysis ²	396/801,041	1.00(referent)	52/72,596	0.93(0.69-1.26)	0.99(0.72-1.34)

¹ Adjusted for age, birth cohort, education, income, body mass index, occupation, smoking status, smoking pack years (men only), alcohol drinking, family history of lung cancer, total energy intake, fruit intake, vegetable intake, total physical activity, hormone replacement therapy (women only), menopausal status (women only).

² Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Type 2 diabetes and lung cancer

Table 3 Hazard ratios for the association between type 2 diabetes and lung cancer risk, stratified by waist to hip ratio, waist circumference, smoking, and menopausal status (women) in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)¹

	No type 2 diabetes		Type 2 diabetes	
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	HR (95%CI) ¹
Men				
Waist to hip ratio ²				
1 st tertile	187/122,101	1.00(referent)	7/5808	0.59(0.27-1.28)
2 nd tertile	129/121,267	1.00(referent)	10/9063	0.67(0.35-1.30)
3 rd tertile	134/111,533	1.00(referent)	25/13,954	1.13(0.71-1.78)
Waist circumference (cm) ³				
<85	163/93,856	1.00(referent)	4/4254	0.38(0.14-1.04)
≥85	287/261,046	1.00(referent)	38/24,571	1.02(0.71-1.46)
Smoking				
Smoking status				
never smoker	53/106,860	1.00(referent)	10/11,199	1.46(0.71-3.02)
former smoker	76/36,466	1.00(referent)	13/4811	0.97(0.52-1.80)
current smoker	321/211,575	1.00(referent)	19/12,815	0.67(0.41-1.10)
Smoking pack years				
0-10	80/147,829	1.00(referent)	11/14,143	1.06(0.54-2.06)
10-20	55/70,068	1.00(referent)	5/4313	0.93(0.36-2.42)
≥20	315/137,004	1.00(referent)	26/10,369	0.78(0.51-1.19)
Women				
Waist to hip ratio ⁴				
1 st tertile	133/282,622	1.00(referent)	2/8367	0.44(0.11-1.80)
2 nd tertile	139/277,675	1.00(referent)	24/20,108	1.37(0.80-2.34)
3 rd tertile	197/240,861	1.00(referent)	30/44,126	0.63(0.40-1.01)
Waist circumference (cm) ⁵				
<80	245/502,838	1.00(referent)	15/20,482	1.01(0.56-1.82)
≥80	224/298,320	1.00(referent)	41/52,119	0.74(0.49-1.13)
Smoking status ⁶				
never smoker	428/781,407	1.00(referent)	50/69,261	0.98(0.72-1.34)
former and current smoker	41/19,751	1.00(referent)	6/3339	0.53(0.21-1.39)
Menopausal status				
Yes	365/365,579	1.00(referent)	49/54,772	0.84(0.61-1.50)
No	104/435,575	1.00(referent)	7/17,828	2.12(0.96-4.67)

¹ The adjusted covariates are as indicated in Table 1.² 1st tertile: <0.878; 2nd tertile: 0.878-0.924; 3rd tertile: ≥0.924.³ A waist circumference ≥ 85cm for men was defined as overweight and central adiposity.⁴ 1st tertile: <0.785; 2nd tertile: 0.785-0.831; 3rd tertile: ≥0.831.

⁵ A waist circumference ≥ 80 cm for women was defined as overweight and central adiposity.

⁶ Due to limited number of former smokers among women, the former and current smokers were combined.

For peer review only

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

	Page	Recommendation
Title and abstract	1-3	(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
Introduction		
Background/rationale	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
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
Variables	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-7	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
Bias	8	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	6-9	(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
Results		
Participants	6-7	(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
Descriptive data	9	(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)
Outcome data	9	Report numbers of outcome events or summary measures over time
Main results	9	(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
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	10	Summarise key results with reference to study objectives
Limitations	11-12	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	10-12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	12	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	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

*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>.

BMJ Open

Preexisting type 2 diabetes and risk of lung cancer: a report from two prospective cohort studies of 133,024 Chinese adults in urban Shanghai

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004875.R1
Article Type:	Research
Date Submitted by the Author:	18-May-2014
Complete List of Authors:	Yang, Wan-Shui; Jiujiang University, Social Science and Public Health Yang, Yang; Shanghai Cancer Institute, Yang, Gong; Vanderbilt School of Medicine, Department of Medicine Chow, Wong-Ho; University of Texas MD Anderson Cancer Center, Li, Honglan; Shanghai Cancer Institute, Department of Epidemiology Gao, Yu-Tang; Shanghai Cancer Institute, Department of Epidemiology Ji, Butian; National Institutes of Health, 3Division of Cancer Epidemiology and Genetics Rothman, Nat; National Cancer Institute, Shu, Xiao-Ou; Vanderbilt School of Medicine, Department of Medicine Zheng, Wei; Vanderbilt School of Medicine, Department of Medicine Xiang, Yong-bing; Shanghai Cancer Institute, Department of Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Oncology, Diabetes and endocrinology
Keywords:	EPIDEMIOLOGY, ONCOLOGY, Epidemiology < ONCOLOGY, Adult oncology < ONCOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Preexisting type 2 diabetes and risk of lung cancer: a report from two prospective cohort studies**
2 **of 133,024 Chinese adults in urban Shanghai**

3 Wan-Shui Yang^{1,2,3}, Yang Yang^{1,2}, Gong Yang⁴, Wong-Ho Chow⁵, Hong-Lan Li¹, Yu-Tang Gao¹,
4 Bu-Tian Ji⁶, Nat Rothman⁶, Wei Zheng⁵, Xiao-Ou Shu⁵, Yong-Bing Xiang^{1,2}

5 **Author affiliations:**

6 1. Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong
7 University School of Medicine, Shanghai, China.

8 2. State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital,
9 Shanghai Jiaotong University School of Medicine, Shanghai, China.

10 3. Department of Social Science and Public Health, School of Basic Medical Science, Jiujiang
11 University, Jiujiang, China.

12 4. Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center,
13 Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, USA.

14 5. Division of Cancer Prevention and Population Sciences, Department of Epidemiology, University
15 of Texas MD Anderson Cancer Center, Houston, Texas, USA.

16 6. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, USA.

17 **Corresponding author:** Prof. Yong-Bing Xiang, Shanghai Cancer Institute, Renji Hospital, Shanghai
18 Jiaotong University School of Medicine, No. 25, Lane 2200, Xie Tu Road, Shanghai 200032, P. R.
19 China, Telephone: 86-21-64437002, Fax: 86-21-64046550, E-mail: ybxiang@shsci.org

20 **Word count:** Text: 3003 words; Abstract: 242 words

21 **Tables: 3 ; Figures: 0**

22 **Keywords:** type 2 diabetes; lung cancer; cohort study; Shanghai

1
2
3 23 **List of abbreviations:** BMI, body mass index ; CI, confidence interval; MET, metabolic equivalents;
4
5 24 HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin-like growth factor; PA, physical
6
7 25 activity; RR, relative risk; SMHS, Shanghai Men’s Health Study; SWHS, Shanghai Women’s Health
8
9
10 26 Study; T2D, type 2 diabetes; WHR, waist-to-hip ratio
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Abstract

Objectives: Observational studies of type 2 diabetes (T2D) and lung cancer risk is limited and controversial. We thus examined the association between T2D and risk of incident lung cancer using a cohort design.

Setting: Data from two ongoing population-based cohorts (the Shanghai Men's Health Study, SMHS, 2002–2006 and the Shanghai Women's Health Study, SWHS, 1996–2000) were used. Cox proportional hazards regression models with T2D as a time-varying exposure were modeled to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Participants: The study population included 61,491 male participants aged 40–74y from Shanghai Men's Health Study and 74,941 female participants aged 40–70y from Shanghai Women's Health Study.

Outcome measure: Lung cancer cases were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics, and were further verified through home visits and review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was used for the present analysis.

Results: After a median follow-up of 6.3 years for SMHS and 12.2 years for SWHS, incident lung cancer case was detected in 492 men and 525 women. A null association between T2D and lung cancer risk was observed in both men (HR=0.87, 95%CI: 0.62–1.21) and women (HR=0.92, 95%CI: 0.69–1.24) after adjustments for potential confounders. Similar results were observed among never smokers.

Conclusions: There is little evidence that preexisting T2D may influence the incidence of lung cancer.

1
2
3 50 **Strengths and limitations of this study**
4
5

- 6 51 ● We showed a null association between type 2 diabetes and risk of lung cancer in two
7
8 52 population-based prospective cohorts with large sample size and long term follow-up.
9
10
11 53 ● This null association was remained after excluding lung cancer cases occurred within the first 3
12
13 54 years after diabetes onset and among never smokers.
14
15
16
17 55 ● However, using self-reported diabetes as exposure, and the lack of pharmacologic data on
18
19 56 diabetes treatments including hypoglycemic agents use and degree of glucose control do not allow
20
21 57 firm conclusions.
22
23
24
25 58

59 Introduction

60 Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer-related
61 death globally and in China¹. The prevalence of diabetes has increased substantially in China, with
62 the age-standardized rates from 2.4% in 1994² to 9.7% in 2007 to 2008³, which may parallel a
63 marked lifestyle transition⁴. Unlike the stable transition in most Western developed countries, these
64 changes have occurred within a very short time in China.

65 Individuals with preexisting type 2 diabetes (T2D) have been shown to be at risk for a number of
66 cancers, including cancers of the liver^{5,6} and pancreas⁷. A link between type 2 diabetes and lung
67 cancer risk has also been suggested, but the evidence is limited and inconsistent. An inverse
68 association was observed in four cohort studies⁸⁻¹¹, whereas an elevated risk of lung cancer was
69 associated with type 2 diabetes in five other cohort studies, particularly among women¹²⁻¹⁶. Other
70 studies, including eight cohort¹⁷⁻²⁴ and two case-control^{25,26} studies, have reported a null association.
71 These discrepancies could be due to a number of factors including insufficient statistical power (small
72 sample size), different study designs and exposure ascertainment, and the lack of adjustments for
73 important covariates such as smoking and body mass index (BMI). On the other hand, all previous
74 studies only considered a single measurement of diabetes at baseline survey, and diabetes newly
75 identified over follow-up periods were neglected, which may have resulted in some underestimation
76 of the true associations. In addition, to our knowledge, no prospective study, to date, has evaluated the
77 effect of diabetes on the lung cancer risk.

78 To further clarify whether type 2 diabetes influence the risk of lung cancer, we assessed the
79 association of type 2 diabetes with the risk of lung cancer by using data from the Shanghai Men's
80 Health Study (SMHS) and the Shanghai Women's Health Study (SWHS), two on-going large

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

81 population-based, prospective cohorts in urban Shanghai, China.

82 **Methods**

83 *Study population*

84 The study population included 61491 male participants of the Shanghai Men's Health Study (SMHS)
85 and 74941 female participants of the Shanghai Women's Health Study (SWHS). Consent has been
86 obtained from each subject after full explanation of the purpose and nature of all procedures used.
87 Details of the study design, scientific rationale, and baseline characteristics of the subjects have been
88 published previously^{27 28}. Briefly, for the SWHS, the recruitment for female residents of Shanghai
89 aged 40-70 years old started in 1996 and was completed in 2000, with an overall participation rate of
90 92.7% (75221/81170). For the SMHS, the recruitment for men aged 40-74 years old with no history of
91 cancer in Shanghai started in April 2002 and was completed in June 2006, with an overall
92 participation rate of 74.1% (61491/83125). Participants were interviewed in person using a structured
93 questionnaire to obtain information on demographic characteristics, lifestyle and dietary habits,
94 medical history, family history of cancer, and other exposures. Anthropometric measurements,
95 including current weight, height, and circumferences of the waist and hip were also taken at baseline.
96 In this analysis, we excluded participants who had a previous history of cancer at enrollment (none for
97 men and n=1598 for women), were younger than 20 years old on the day of diabetes diagnosis to
98 reduce potential bias from including patients with type 1 diabetes (n=3 for men and 3 for women),
99 died of cancers of unknown origin or without diagnosis date (n=126 for men and n=114 for women),
100 had missing values for any of the covariates of interest (n=1458 for men and n=109 for women), and
101 was diagnosed with lung cancer before the diagnosis of diabetes (n=1 for men and n=3 for women).
102 After exclusion, a total of 59,910 men and 73,114 women remained in current analysis.

1
2 103 ***Diabetes assessment***
3
4

5 104 In our analysis, diabetes cases were identified based completely on the self-reported data.
6
7
8 105 Self-reported diabetes was recorded on the baseline questionnaires (2002–2006 for the SMHS and
9
10 106 1996–2000 for the SWHS), and updated in each of the subsequent follow-up questionnaires
11
12
13 107 (2004–2008 for the SMHS, and 2000–2002, 2002–2004 and 2004–2007 for the SWHS). Participants
14
15 108 were asked whether they had ever been diagnosed with DM by a physician (yes/no) and if yes, the age
16
17
18 109 at diagnosis was recorded. From the beginning with the 2004–2008 follow-up questionnaires for men
19
20 110 and 2000–2002 follow-up questionnaires for women, and for all subsequent surveys, the question was
21
22
23 111 modified, and participants were additionally asked in what year and month and in which hospital their
24
25 112 diabetes had been diagnosed since the most recent survey.
26
27

28
29 113 In present study, a case of T2D was considered to be confirmed if the participant reported having been
30
31 114 diagnosed with type 2 diabetes and met at least one of the following self-reported items: (i) fasting
32
33 115 plasma glucose concentration is greater than 7 mmol/l on two separate occasions, (ii) plasma glucose
34
35 116 concentration is greater than 11.1 mmol/l at 2 h for a 75 g oral glucose tolerance test and (iii) the use
36
37
38 117 of insulin or other hypoglycemic agents. A validation study showed that the self-reported diabetes was
39
40 118 in good agreement with the measurement of fasting plasma glucose concentration and medical
41
42
43 119 treatment records in our cohorts (data was not shown).
44
45

46
47 120 ***Follow up and outcome ascertainment***
48
49

50 121 The participants were followed up with home visits every 2 to 3 years to update exposure information
51
52 122 and to ascertain new diagnosis of cancers. For the SMHS, the first follow up interview was conducted
53
54
55 123 from 2004-2008 with a response rate of 97.6%. For the SWHS, the first, second and third follow ups
56
57
58 124 were conducted from 2000-2002, 2002-2004 and 2004-2007 with corresponding response rates of
59
60

125 99.8%, 98.7% and 96.7%, respectively.

126 The incident lung cancer cases were defined as a primary tumor with an International Classification of

127 Diseases (ICD)-9 code 162, and were identified through annual record linkage to the Shanghai Cancer

128 Registry and Shanghai Municipal Registry of Vital Statistics. All possible cancer cases were verified

129 through home visits and further review of medical charts by clinical and/or pathological experts.

130 Outcome data through December 31, 2010 for both men and women was used for the present analysis,

131 with median follow-up periods of 6.3 years and 12.2 years for SMHS and SWHS, respectively.

132 *Statistical analysis*

133 Cox proportional hazards regression models with age as time scale were used to calculate age-adjusted

134 and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations

135 of type 2 diabetes with the risk of incident lung cancer. Type 2 diabetes (yes/no) was modeled as a

136 time-varying exposure in the current study, meaning that information on type 2 diabetes reported in

137 questionnaire n , was used to prospectively categorize participants for the periods between completion

138 of questionnaires n and $n + 1$, and the risk person-years was allocated to the corresponding groups, the

139 corresponding method was described elsewhere in detail ⁵.

140 Covariates were selected based on their potential to confound or modify the association between type

141 2 diabetes and lung cancer. All covariates were modeled using baseline values. The covariates

142 included in the multivariate-adjusted models were age (less than 50y, 50-60y, more than 60y), birth

143 cohort (1920s, 1930s, 1940s, 1950s, 1960s), education (illiteracy or elementary school, middle school,

144 high school, graduate school), income (low, low to middle, middle to high, high) (see Table 1), body

145 mass index (BMI; less than 18.5, 18.5-24, 24-28, more than 28, according to Chinese standard ²⁹),

146 occupation [housewife (women only), manual, clerical, and professional], smoking status (never

1
2 147 smoking, ever smoking, current smoking, for men), smoking pack-years (0-10, 10-20, more than 20,
3
4
5 148 for men), ever smoking (yes/no, for women), alcohol drinking(0, 0-1.5, more than 1.5, drink/day, for
6
7 149 men), ever alcohol drinking (yes/no, for women), family history of cancer (yes/no), total energy intake
8
9
10 150 (kcal/day, quartiles), fruit intake (g/day, quartiles), vegetable intake (g/day, quartiles), total physical
11
12 151 activity [PA; standard metabolic equivalents (METs) as MET-hr/day in quartiles; 1 MET-hr=15
13
14 152 minutes of moderate intensity activity]^{30 31}, history of hepatitis/chronic liver disease (yes/no),
15
16
17 153 hormone replacement therapy (HRT; yes/no for women only), menopausal status
18
19
20 154 (pre-/post-menopausal for women only).

21
22
23 155 We also tested for potential interactions of diabetes with age, income, education, occupation, family
24
25 156 history of lung cancer, alcohol drinking, physical activity, and smoking, by comparing the Cox models
26
27
28 157 with and without the interaction terms using a likelihood ratio test. In testing of the proportional
29
30 158 hazard assumption by creating interaction of diabetes and a logarithm of time in the model, we found
31
32
33 159 no violation of proportionality.

34
35
36 160 To investigate the potential effect for over detection bias (i.e. the increased detection around the time
37
38 161 of type 2 diabetes diagnosis), age-adjusted incidence rates by different time intervals of follow-up
39
40 162 (0-1, 1-3, more than 3 years) in diabetes cohort and no-diabetes cohort were calculated for lung
41
42
43 163 cancer, which were directly standardized by the entire cohort population. To examine whether
44
45
46 164 diabetes treatments affect the risk of lung cancer associated with T2D, a separate analysis that
47
48
49 165 excluded treated diabetes was conducted.

50
51
52 166 All data analyses were performed with SAS 9.2 (SAS Institute, Cary, NC), and a two-sided *P* value of
53
54 167 0.05 was considered statistically significant if not specified.

57 168 **Results**

Results from the SMHS and SWHS

The distributions of selected baseline characteristics according to type 2 diabetes are shown in Table 1. In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with type 2 diabetes at baseline or during follow up periods. Compared to men and women without diabetes, patients with type 2 diabetes were older and had higher BMI, greater intake of total energy and vegetable, but less fruit consumption and alcohol drinking at baseline. In SWHS, less than 2.8% of the women reported ever smoking.

Through December 31, 2010, incident lung cancer case was detected in 492 men and 525 women. For men, the age-standardized incidence rates (1/100 000 person-years) of lung cancer were 87.48, 20.73, and 161.92 for 0-1, 1-3, more than 3 years following the diabetes index date in diabetes cohort, respectively; 112.97, 119.57, and 141.81 for 0-1, 1-3, more than 3 years since baseline interview for the cohort without diabetes, respectively. For women, the age-standardized incidence rates (1/100 000 person-years) were 80.53, 19.81, 72.85 for 0-1, 1-3, more than 3 years following the diabetes index date in diabetes cohort, respectively; and 29.68, 41.43, 69.46 for 0-1, 1-3, more than 3 years since baseline interview for non-diabetes cohort, respectively.

After adjustments for smoking, BMI, alcohol drinking, and other factors, type 2 diabetes was not associated with the risk of developing lung cancer either in men (HR=0.87, 95%CI: 0.62-1.21) or in women (HR=0.93, 95%CI: 0.69-1.25) (Table 2). This null association remained when the analysis was restricted to never smokers (Table 3) or after excluding lung cancer cases diagnosed within the first 3 years after diabetes diagnosis (Table 2). Results from subgroup analysis by waist to hip ratio, waist circumference, smoking, and menopausal status (women) did not appreciably alter the main results (Table 3). We did not observe effect modification by age, income, education, occupation, family

1
2 191 history of lung cancer, alcohol drinking, or physical activity. In addition, an additional analysis that
3
4
5 192 excluded treated diabetes also showed a null association between untreated diabetes and lung cancer
6
7 193 (data not shown).
8
9

10 194 **Discussion**

11
12
13
14 195 No observational study, to our knowledge, has investigated lung cancer risk in relation to type 2
15
16 196 diabetes in mainland China to date. Findings from our population-based cohort study suggested that
17
18 197 type 2 diabetes is not associated with the risk of incident lung cancer among Chinese adults. This null
19
20
21 198 association remained regardless of age, income, education, occupation, family history of lung cancer,
22
23
24 199 alcohol drinking, physical activity, smoking status, menopausal status, and WHR in stratified analysis.

25
26
27 200 Previous epidemiological studies on type 2 diabetes and lung cancer yielded conflicting results,
28
29 201 varying from a positive ^{16 32}, null ^{17 19-22 24 33-35} to an inverse ⁹⁻¹¹ association. Differing study design,
30
31 202 sample size or follow up time, and covariates adjustments may, in part, explain this inconsistency. A
32
33
34 203 comparative study ⁸ and 3 cohort studies ⁹⁻¹¹ without adjustments for smoking concluded an inverse
35
36
37 204 association; two cohort studies that reported a positive association have not adjusted for BMI ¹⁶ or
38
39 205 smoking ³²; two studies ^{25 26} with a null association used case-control design; three studies have a
40
41 206 limited follow up periods (<5y) ^{11 21} or sample size (<10,000) ¹⁵. Consistent with most pertinent
42
43
44 207 studies ^{17 19-22 24 33-35}, we observed a null association between type 2 diabetes and lung cancer risk
45
46
47 208 overall and among nonsmoking participants.

48
49
50 209 Although a null association was found between T2D and lung cancer, previous observational studies
51
52 210 have inconsistently shown the increased risk of incident several cancers among individuals with type 2
53
54
55 211 diabetes, including cancers of liver ^{5 6} and pancreas ⁷. The potential biologic links between diabetes
56
57
58 212 and cancer risk included hyperinsulinemia (either endogenous due to insulin resistance or exogenous

1
2 213 due to administered insulin or insulin secretagogues), hyperglycemia, and/or chronic inflammation³⁶.
3
4
5 214 The hyperinsulinemia may involve in carcinogenesis by its mitogenic effect via the insulin/
6
7 215 insulin-like growth factor (IGF) axis³⁶. On the other hand, hyperglycemia may cause an abnormal
8
9
10 216 energy balance and impair the effect of ascorbic acid on the intracellular metabolism and reduce the
11
12 217 effectiveness of the immune system³⁷, which could favor cancer incidence and progression in diabetic
13
14
15 218 patients. In addition, free fatty acids, interleukin-6, monocyte chemoattractant protein, plasminogen
16
17 219 activator inhibitor-1, adiponectin, leptin, and tumor necrosis factor- α , which were produced by
18
19
20 220 adipose tissue among T2D related obesity, may play an etiologic role in regulating malignant
21
22 221 transformation or cancer progression³⁶.
23
24
25 222 Strengths of our study include the population-based cohort design, large sample size, high response
26
27
28 223 rates of follow ups (over 96% for in-person home visits), and the use of repeated measures of diabetes
29
30
31 224 status. However, several limitations to this study should be noted. As diabetes were self-reported and a
32
33 225 number of patients with diabetes did not know they had the disease³⁸, the misclassification of type 2
34
35
36 226 diabetes cannot be ruled out and could be non-differential, thus led to the underestimation of the true
37
38 227 association. Nevertheless, we observed a high agreement between self-report data and data from
39
40
41 228 medical records and laboratory test for T2D in a random sample of subjects from our cohorts. Also,
42
43 229 previous validation studies^{39 40} indicated that a self-reported history of diabetes could be reasonably
44
45
46 230 accurate and could provide a useful assessment for broad measures of diabetes in the large-scale
47
48 231 observational study.
49
50
51 232 In addition, the findings from SWHS would have been affected by over-detection bias, given higher
52
53
54 233 incidence rate of lung cancer in the first year following the diabetes index date compared to those
55
56 234 without diabetes regardless of different time intervals of follow-up. However, the results were
57
58
59
60

1
2 235 unchanged in the analysis after excluding lung cancer cases occurred within the first 3 years after
3
4
5 236 diabetes onset. Moreover, this potential increased ascertainment in diabetics is unlikely to occur in
6
7 237 SMHS because of the lower incidence rate of lung cancer in the diabetic cohort within the first year
8
9
10 238 after the diabetes diagnosis.
11
12
13 239 Other limitations to the study include the lack of pharmacologic data on diabetes treatments, including
14
15 240 hypoglycemic agents use and degree of glucose control. However, sensitivity analysis showed a
16
17
18 241 similarly null association between untreated diabetes and risk of lung cancer, indicating that the
19
20 242 diabetes treatments may not affect our main results. Whereas this finding should be interpreted with
21
22
23 243 cautions because the information for the history of hypoglycemic drug use were also on the basis of
24
25 244 self-reported data in our study.
26
27
28 245 In summary, our cohort study indicated that type 2 diabetes is not associated with lung cancer risk.
29
30
31 246 Future research to find other modifiable risk factors for lung cancer should be warranted.
32
33
34 247
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

248 **Acknowledgements** We would like to thank the participants of the Shanghai Men's Health Study and
249 the Shanghai Women's Health Study for the invaluable contribution to this work.

250 **Contributions** YBX contributed to the conception and design of the study; YBX, HLL and YTG
251 acquired data; WSY, YY and YBX performed the statistical analysis and the interpretation of results;
252 WSY wrote the first draft; All authors contributed to the critical review of the manuscript and
253 approved the final manuscript; The corresponding author (YBX) had full access to all of the data and
254 the final responsibility for the decision to submit for publication.

255 **Funding** This work was supported by the US National Institutes of Health (grant number R37
256 CA070867 and R01 CA82729); the fund of Key Discipline and Specialty Foundation of Shanghai
257 Municipal Commission of Health and Family Planning.

258 **Competing interests** None. The funding sponsor had no role in the study design, data collection,
259 statistical analysis and result interpretation, as well as in the writing of the report and the decision to
260 submit for publication. The corresponding author had full access to all data in the study and final
261 responsibility for the decision to submit for publication.

262 **Study approval** Institutional review board.

263 **Ethics approval** IRBs of Vanderbilt University (USA) and Shanghai Cancer Institute (China).

264 **Data sharing** No additional unpublished data.

265 **Reference**

- 266 1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;**61**(2):69-90.
- 267 2. Pan XR, Yang WY, Li GW, et al. Prevalence of diabetes and its risk factors in China, 1994. National
268 Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997;**20**(11):1664-9.
- 269 3. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med*
270 2010;**362**(12):1090-101.
- 271 4. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care*
272 2011;**34**(6):1249-57.
- 273 5. Yang WS, Shu XO, Gao J, et al. Prospective evaluation of type 2 diabetes mellitus on the risk of
274 primary liver cancer in Chinese men and women. *Ann Oncol* 2013;**24**(6):1679-85.
- 275 6. Yang WS, Va P, Bray F, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma
276 occurrence and prognosis: a meta-analysis of prospective cohort studies. *PLoS One*
277 2011;**6**(12):e27326.
- 278 7. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of
279 cohort studies. *Eur J Cancer* 2011;**47**(13):1928-37.
- 280 8. Armstrong B, Lea AJ, Adelstein AM, et al. Cancer mortality and saccharin consumption in diabetics.
281 *Br J Prev Soc Med* 1976;**30**(3):151-7.
- 282 9. Atchison EA, Gridley G, Carreon JD, et al. Risk of cancer in a large cohort of U.S. veterans with
283 diabetes. *Int J Cancer* 2011;**128**(3):635-43.
- 284 10. Lo SF, Chang SN, Muo CH, et al. Modest increase in risk of specific types of cancer types in type
285 2 diabetes mellitus patients. *Int J Cancer* 2013;**132**(1):182-8.
- 286 11. Ogunleye AA, Ogston SA, Morris AD, et al. A cohort study of the risk of cancer associated with
287 type 2 diabetes. *Br J Cancer* 2009;**101**(7):1199-201.

- 1
2 288 12. Emerging Risk Factors C, Seshasai SR, Kaptoge S, et al. Diabetes mellitus, fasting glucose, and
3
4 289 risk of cause-specific death. *N Engl J Med* 2011;**364**(9):829-41.
5
6
7 290 13. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese
8
9 291 men and women. *Eur J Cancer Prev* 2007;**16**(1):83-9.
10
11
12 292 14. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and
13
14 293 insulin effects. *Diabetologia* 2012;**55**(4):948-58.
15
16
17 294 15. Luo J, Chlebowski R, Wactawski-Wende J, et al. Diabetes and lung cancer among postmenopausal
18
19 295 women. *Diabetes Care* 2012;**35**(7):1485-91.
20
21
22 296 16. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and
23
24 297 women. *JAMA* 2005;**293**(2):194-202.
25
26
27 298 17. Coughlin SS, Calle EE, Teras LR, et al. Diabetes mellitus as a predictor of cancer mortality in a
28
29 299 large cohort of US adults. *Am J Epidemiol* 2004;**159**(12):1160-7.
30
31
32 300 18. Saydah SH, Loria CM, Eberhardt MS, et al. Abnormal glucose tolerance and the risk of cancer
33
34 301 death in the United States. *Am J Epidemiol* 2003;**157**(12):1092-100.
35
36
37 302 19. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer: results from a
38
39 303 large-scale population-based cohort study in Japan. *Arch Intern Med* 2006;**166**(17):1871-7.
40
41
42 304 20. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I.
43
44 305 Follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiol*
45
46 306 *Biomarkers Prev* 1995;**4**(8):807-11.
47
48
49 307 21. Hall GC, Roberts CM, Boulis M, et al. Diabetes and the risk of lung cancer. *Diabetes Care*
50
51 308 2005;**28**(3):590-4.
52
53
54
55 309 22. Khan M, Mori M, Fujino Y, et al. Site-specific cancer risk due to diabetes mellitus history:
56
57 310 evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev*

- 1
2 311 2006;7(2):253-9.
3
4
5 312 23. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than
6
7 313 140,000 adults in Austria. *Diabetologia* 2006;**49**(5):945-52.
8
9
10 314 24. Stattin P, Bjor O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes*
11
12 315 *Care* 2007;**30**(3):561-7.
13
14
15 316 25. Rousseau MC, Parent ME, Pollak MN, et al. Diabetes mellitus and cancer risk in a
16
17 317 population-based case-control study among men from Montreal, Canada. *Int J Cancer*
18
19 318 2006;**118**(8):2105-9.
20
21
22 319 26. O'Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control
23
24 320 study. *J Chronic Dis* 1985;**38**(5):435-41.
25
26
27 321 27. Villegas R, Yang G, Liu D, et al. Validity and reproducibility of the food-frequency questionnaire
28
29 322 used in the Shanghai men's health study. *Br J Nutr* 2007;**97**(5):993-1000.
30
31
32 323 28. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design,
33
34 324 and baseline characteristics. *Am J Epidemiol* 2005;**162**(11):1123-31.
35
36
37 325 29. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive
38
39 326 values of body mass index and waist circumference for risk factors of certain related diseases
40
41 327 in Chinese adults--study on optimal cut-off points of body mass index and waist circumference
42
43 328 in Chinese adults. *Biomed Environ Sci* 2002;**15**(1):83-96.
44
45
46
47 329 30. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of
48
49 330 activity codes and MET intensities. *Med Sci Sports Exerc* 2000;**32**(9 Suppl):S498-504.
50
51
52 331 31. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of
53
54 332 energy costs of human physical activities. *Med Sci Sports Exerc* 1993;**25**(1):71-80.
55
56
57 333 32. Chodick G, Heymann AD, Rosenmann L, et al. Diabetes and risk of incident cancer: a large
58
59
60

- 1
2 334 population-based cohort study in Israel. *Cancer Causes Control* 2010;**21**(6):879-87.
- 3
4 335 33. Ehrlich SF, Quesenberry CP, Jr., Van Den Eeden SK, et al. Patients diagnosed with diabetes are at
5
6
7 336 increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and
8
9
10 337 pneumonia but not lung cancer. *Diabetes Care* 2010;**33**(1):55-60.
- 11
12 338 34. Wotton CJ, Yeates DG, Goldacre MJ. Cancer in patients admitted to hospital with diabetes mellitus
13
14
15 339 aged 30 years and over: record linkage studies. *Diabetologia* 2011;**54**(3):527-34.
- 16
17 340 35. Yeh HC, Platz EA, Wang NY, et al. A prospective study of the associations between treated
18
19
20 341 diabetes and cancer outcomes. *Diabetes Care* 2012;**35**(1):113-8.
- 21
22 342 36. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes*
23
24
25 343 *Care* 2010;**33**(7):1674-85.
- 26
27 344 37. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. *Endocr Relat Cancer*
28
29
30 345 2009;**16**(4):1103-23.
- 31
32 346 38. Li R, Lu W, Jiang QW, et al. Increasing prevalence of type 2 diabetes in Chinese adults in
33
34
35 347 Shanghai. *Diabetes Care* 2012;**35**(5):1028-30.
- 36
37 348 39. Martin LM, Leff M, Calonge N, et al. Validation of self-reported chronic conditions and health
38
39
40 349 services in a managed care population. *Am J Prev Med* 2000;**18**(3):215-8.
- 41
42 350 40. Wu SC, Li CY, Ke DS. The agreement between self-reporting and clinical diagnosis for selected
43
44
45 351 medical conditions among the elderly in Taiwan. *Public Health* 2000;**114**(2):137-42.
- 46
47 352
48
49 353
50
51
52
53
54
55
56
57
58
59
60

Type 2 diabetes and lung cancer

Table 1 Characteristics of study participants according to type 2 diabetes status in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)¹

	Men		Women	
	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes
Number of subjects	55311	4599	66,823	6291
Age at baseline (y)	54.89 (9.63)	60.48 (9.61)	51.94 (8.91)	58.51 (8.34)
Education level (%)				
Illiteracy or elementary school	6.27	11.33	19.28	43.18
Middle school	33.51	33.57	37.95	29.27
High school	36.69	29.53	28.85	18.41
Graduate school/College	23.52	25.57	13.92	9.14
Income (%) ²				
Low	12.86	9.24	15.58	21.43
Low-middle	77.45	80.82	38.08	39.88
Middle-high	8.93	9.26	28.47	24.34
High	0.76	0.68	17.87	14.35
Occupation (%)				
Housewife	-	-	0.34	0.64
Professional	25.79	31.92	29.98	22.78
Clerical	21.92	22.53	20.81	20.32
Manual worker	52.29	45.55	49.87	56.26
BMI kg/m ²	23.64 (3.07)	24.61 (3.04)	23.82 (3.33)	26.00 (3.76)
BMI (%)				
Less than 18.5	4.49	1.48	3.58	1.30
18.5-24.0	50.79	43.23	51.82	29.08
24.0-28.0	37.01	41.47	33.83	42.39
Great than 28	7.71	13.83	10.77	27.23
Smoking status (%)				
Never smokers	29.69	38.16	97.47	95.25
Former smokers	10.29	17.33		
Current smokers	60.02	44.51	2.59 ³	4.75 ³
Physical activity (MET hours/week)	59.56 (34.03)	61.04 (35.83)	107.00 (45.30)	102.50 (43.31)
Ever alcohol intake (%)	34.82	29.03	2.29	1.87
Total energy intake (Kcal/day)	8029.80 (2029.10)	7481.00 (1929.50)	7033.90 (1681.10)	6845.10 (1842.40)
Fruit intake (g/day)	155.10 (125.00)	98.58 (110.50)	271.90 (178.30)	187.90 (175.30)
Vegetable intake (g/day)	341.20 (190.10)	373.20 (218.40)	295.70 (168.70)	305.70 (188.70)
Family history of cancer (%)	28.27	30.03	26.48	26.61
Post-menopausal (%)	-	-	46.27	76.58
HRT use (%)	-	-	2.07	2.10

¹ Abbreviations: BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-hr=15 minutes of moderate intensity activity); HRT, hormone replacement therapy. Continuous variables are presented as the mean (the standard deviation).

² Low: less than 10,000 Yuan per family per year for women and less than 1000 Yuan per person per month for men; Low to middle: 10,000 - 19,999 Yuan per family per year for women and 1000-3000 Yuan per person per month for men; Middle to high: 20,000-29,999 Yuan per family per year for women and 3000-5000 Yuan per person per month for men; High: greater

1
2 than 30,000 Yuan per family per year for women and more than 5000 Yuan per person per month for men.

3 ³ Due to small number of smokers among women, the number of current and former smokers was combined.
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Type 2 diabetes and lung cancer

Table 2 Hazard ratios for the association between type 2 diabetes and lung cancer risk in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)

	No type 2 diabetes		Type 2 diabetes		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) ¹
Men					
Entire cohort	450/354,902	1.00(referent)	42/28,825	0.80(0.58-1.10)	0.87(0.62-1.21)
Sensitivity analysis ²	260/354,604	1.00(referent)	28/28,805	0.94(0.64-1.39)	1.10(0.73-1.64)
Women					
Entire cohort	469/801,158	1.00(referent)	56/72,600	0.88(0.66-1.18)	0.93(0.69-1.25)
Sensitivity analysis ²	396/801,041	1.00(referent)	52/72,596	0.93(0.69-1.26)	0.99(0.72-1.34)

¹ Adjusted for age, birth cohort, education, income, body mass index, occupation, smoking status, smoking pack years (men only), alcohol drinking, family history of lung cancer, total energy intake, fruit intake, vegetable intake, total physical activity, hormone replacement therapy (women only), menopausal status (women only).

² Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Type 2 diabetes and lung cancer

Table 3 Hazard ratios for the association between type 2 diabetes and lung cancer risk, stratified by waist to hip ratio, waist circumference, smoking, and menopausal status (women) in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)¹

	No type 2 diabetes		Type 2 diabetes	
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	HR (95%CI) ¹
Men				
Waist to hip ratio ²				
1 st tertile	187/122,101	1.00(referent)	7/5808	0.59(0.27-1.28)
2 nd tertile	129/121,267	1.00(referent)	10/9063	0.67(0.35-1.30)
3 rd tertile	134/111,533	1.00(referent)	25/13,954	1.13(0.71-1.78)
Waist circumference (cm) ³				
Less than 85	163/93,856	1.00(referent)	4/4254	0.38(0.14-1.04)
Greater than 85	287/261,046	1.00(referent)	38/24,571	1.02(0.71-1.46)
Smoking				
Smoking status				
never smoker	53/106,860	1.00(referent)	10/11,199	1.46(0.71-3.02)
former smoker	76/36,466	1.00(referent)	13/4811	0.97(0.52-1.80)
current smoker	321/211,575	1.00(referent)	19/12,815	0.67(0.41-1.10)
Smoking pack years				
0-10	80/147,829	1.00(referent)	11/14,143	1.06(0.54-2.06)
10-20	55/70,068	1.00(referent)	5/4313	0.93(0.36-2.42)
Greater than 20	315/137,004	1.00(referent)	26/10,369	0.78(0.51-1.19)
Women				
Waist to hip ratio ⁴				
1 st tertile	133/282,622	1.00(referent)	2/8367	0.44(0.11-1.80)
2 nd tertile	139/277,675	1.00(referent)	24/20,108	1.37(0.80-2.34)
3 rd tertile	197/240,861	1.00(referent)	30/44,126	0.63(0.40-1.01)
Waist circumference (cm) ⁵				
Less than 80	245/502,838	1.00(referent)	15/20,482	1.01(0.56-1.82)
More than 80	224/298,320	1.00(referent)	41/52,119	0.74(0.49-1.13)
Smoking status ⁶				
never smoker	428/781,407	1.00(referent)	50/69,261	0.98(0.72-1.34)
former and current smoker	41/19,751	1.00(referent)	6/3339	0.53(0.21-1.39)
Menopausal status				
Yes	365/365,579	1.00(referent)	49/54,772	0.84(0.61-1.50)
No	104/435,575	1.00(referent)	7/17,828	2.12(0.96-4.67)

¹ The adjusted covariates are as indicated in Table 1.² 1st tertile: <0.878; 2nd tertile: 0.878-0.924; 3rd tertile: ≥0.924.³ A waist circumference ≥ 85cm for men was defined as overweight and central adiposity.⁴ 1st tertile: <0.785; 2nd tertile: 0.785-0.831; 3rd tertile: ≥0.831.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

⁵ A waist circumference ≥ 80 cm for women was defined as overweight and central adiposity.

⁶ Due to limited number of former smokers among women, the former and current smokers were combined.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Preexisting type 2 diabetes and risk of lung cancer: a report from two prospective cohort studies**
2 **of 133,024 Chinese adults in urban Shanghai**

3 Wan-Shui Yang^{1,2,3}, Yang Yang^{1,2}, Gong Yang⁴, Wong-Ho Chow⁵, Hong-Lan Li¹, Yu-Tang Gao¹,
4 Bu-Tian Ji⁶, Nat Rothman⁶, Wei Zheng⁵, Xiao-Ou Shu⁵, Yong-Bing Xiang^{1,2}

5 **Author affiliations:**

6 1. Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong
7 University School of Medicine, Shanghai, China.

8 2. State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital,
9 Shanghai Jiaotong University School of Medicine, Shanghai, China.

10 3. Department of Social Science and Public Health, School of Basic Medical Science, Jiujiang
11 University, Jiujiang, China.

12 4. Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center,
13 Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, USA.

14 5. Division of Cancer Prevention and Population Sciences, Department of Epidemiology, University
15 of Texas MD Anderson Cancer Center, Houston, Texas, USA.

16 6. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, USA.

17 **Corresponding author:** Prof. Yong-Bing Xiang, Shanghai Cancer Institute, Renji Hospital, Shanghai
18 Jiaotong University School of Medicine, No. 25, Lane 2200, Xie Tu Road, Shanghai 200032, P. R.
19 China, Telephone: 86-21-64437002, Fax: 86-21-64046550, E-mail: ybxiang@shsci.org

20 **Word count:** Text: 3003 words; Abstract: 242 words

21 **Tables: 3 ; Figures: 0**

22 **Keywords:** type 2 diabetes; lung cancer; cohort study; Shanghai

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27

List of abbreviations: BMI, body mass index ; CI, confidence interval; MET, metabolic equivalents; HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin-like growth factor; PA, physical activity; RR, relative risk; SMHS, Shanghai Men’s Health Study; SWHS, Shanghai Women’s Health Study; T2D, type 2 diabetes; WHR, waist-to-hip ratio

For peer review only

Abstract

Objectives: Observational studies of type 2 diabetes (T2D) and lung cancer risk is limited and controversial. We thus examined the association between T2D and risk of incident lung cancer using a cohort design.

Setting: Data from two ongoing population-based cohorts (the Shanghai Men's Health Study, SMHS, 2002–2006 and the Shanghai Women's Health Study, SWHS, 1996–2000) were used. Cox proportional hazards regression models with T2D as a time-varying exposure were modeled to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Participants: The study population included 61,491 male participants aged 40–74y from Shanghai Men's Health Study and 74,941 female participants aged 40–70y from Shanghai Women's Health Study.

Outcome measure: Lung cancer cases were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics, and were further verified through home visits and review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was used for the present analysis.

Results: After a median follow-up of 6.3 years for SMHS and 12.2 years for SWHS, incident lung cancer case was detected in 492 men and 525 women. A null association between T2D and lung cancer risk was observed in both men (HR=0.87, 95%CI: 0.62–1.21) and women (HR=0.92, 95%CI: 0.69–1.24) after adjustments for potential confounders. Similar results were observed among never smokers.

Conclusions: There is little evidence that preexisting T2D may influence the incidence of lung cancer.

1
2
3 50 **Strengths and limitations of this study**
4
5

- 6 51 ● We showed a null association between type 2 diabetes and risk of lung cancer in two
7
8 52 population-based prospective cohorts with large sample size and long term follow-up.
9
10
11 53 ● This null association was remained after excluding lung cancer cases occurred within the first 3
12
13 54 years after diabetes onset and among never smokers.
14
15
16
17 55 ● However, using self-reported diabetes as exposure, and the lack of pharmacologic data on
18
19 56 diabetes treatments including hypoglycemic agents use and degree of glucose control do not allow
20
21 57 firm conclusions.
22
23
24
25 58

59 Introduction

60 Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer-related
61 death globally and in China ¹. The prevalence of diabetes has increased substantially in China, with
62 the age-standardized rates from 2.4% in 1994 ² to 9.7% in 2007 to 2008 ³, which may parallel a
63 marked lifestyle transition ⁴. Unlike the stable transition in most Western developed countries, these
64 changes have occurred within a very short time in China.

65 Individuals with preexisting type 2 diabetes (T2D) have been shown to be at risk for a number of
66 cancers, including cancers of the liver ^{5,6} and pancreas ⁷. A link between type 2 diabetes and lung
67 cancer risk has also been suggested, but the evidence is limited and inconsistent. An inverse
68 association was observed in four cohort studies ⁸⁻¹¹, whereas an elevated risk of lung cancer was
69 associated with type 2 diabetes in five other cohort studies, particularly among women ¹²⁻¹⁶. Other
70 studies, including eight cohort ¹⁷⁻²⁴ and two case-control ^{25,26} studies, have reported a null association.
71 These discrepancies could be due to a number of factors including insufficient statistical power (small
72 sample size), different study designs and exposure ascertainment, and the lack of adjustments for
73 important covariates such as smoking and body mass index (BMI). On the other hand, all previous
74 studies only considered a single measurement of diabetes at baseline survey, and diabetes newly
75 identified over follow-up periods were neglected, which may have resulted in some underestimation
76 of the true associations. In addition, to our knowledge, no prospective study, to date, has evaluated the
77 effect of diabetes on the lung cancer risk.

78 To further clarify whether type 2 diabetes influence the risk of lung cancer, we assessed the
79 association of type 2 diabetes with the risk of lung cancer by using data from the Shanghai Men's
80 Health Study (SMHS) and the Shanghai Women's Health Study (SWHS), two on-going large

1
2 81 population-based, prospective cohorts in urban Shanghai, China.

3
4
5 82 **Methods**

6
7 83 ***Study population***

8
9
10 84 The study population included 61491 male participants of the Shanghai Men's Health Study (SMHS)
11
12 85 and 74941 female participants of the Shanghai Women's Health Study (SWHS). Consent has been
13
14 86 obtained from each subject after full explanation of the purpose and nature of all procedures used.
15
16
17 87 Details of the study design, scientific rationale, and baseline characteristics of the subjects have been
18
19 88 published previously^{27 28}. Briefly, for the SWHS, the recruitment for female residents of Shanghai
20
21 89 aged 40-70 years old started in 1996 and was completed in 2000, with an overall participation rate of
22
23 90 92.7% (75221/81170). For the SMHS, the recruitment for men aged 40-74 years old with no history of
24
25 91 cancer in Shanghai started in April 2002 and was completed in June 2006, with an overall
26
27 92 participation rate of 74.1% (61491/83125). Participants were interviewed in person using a structured
28
29 93 questionnaire to obtain information on demographic characteristics, lifestyle and dietary habits,
30
31 94 medical history, family history of cancer, and other exposures. Anthropometric measurements,
32
33 95 including current weight, height, and circumferences of the waist and hip were also taken at baseline.
34
35
36 96 In this analysis, we excluded participants who had a previous history of cancer at enrollment (none for
37
38 97 men and n=1598 for women), were younger than 20 years old on the day of diabetes diagnosis to
39
40 98 reduce potential bias from including patients with type 1 diabetes (n=3 for men and 3 for women),
41
42 99 died of cancers of unknown origin or without diagnosis date (n=126 for men and n=114 for women),
43
44 100 had missing values for any of the covariates of interest (n=1458 for men and n=109 for women), and
45
46 101 was diagnosed with lung cancer before the diagnosis of diabetes (n=1 for men and n=3 for women).
47
48
49 102 After exclusion, a total of 59,910 men and 73,114 women remained in current analysis.
50
51
52
53
54
55
56
57
58
59
60

Diabetes assessment

In our analysis, diabetes cases were identified based completely on the self-reported data. Self-reported diabetes was recorded on the baseline questionnaires (2002–2006 for the SMHS and 1996–2000 for the SWHS), and updated in each of the subsequent follow-up questionnaires (2004–2008 for the SMHS, and 2000–2002, 2002–2004 and 2004–2007 for the SWHS). Participants were asked whether they had ever been diagnosed with DM by a physician (yes/no) and if yes, the age at diagnosis was recorded. From the beginning with the 2004–2008 follow-up questionnaires for men and 2000–2002 follow-up questionnaires for women, and for all subsequent surveys, the question was modified, and participants were additionally asked in what year and month and in which hospital their diabetes had been diagnosed since the most recent survey.

In present study, a case of T2D was considered to be confirmed if the participant reported having been diagnosed with type 2 diabetes and met at least one of the following self-reported items: (i) fasting plasma glucose concentration is greater than 7 mmol/l on two separate occasions, (ii) plasma glucose concentration is greater than 11.1 mmol/l at 2 h for a 75 g oral glucose tolerance test and (iii) the use of insulin or other hypoglycemic agents. A validation study showed that the self-reported diabetes was in good agreement with the measurement of fasting plasma glucose concentration and medical treatment records in our cohorts (data was not shown).

Follow up and outcome ascertainment

The participants were followed up with home visits every 2 to 3 years to update exposure information and to ascertain new diagnosis of cancers. For the SMHS, the first follow up interview was conducted from 2004-2008 with a response rate of 97.6%. For the SWHS, the first, second and third follow ups were conducted from 2000-2002, 2002-2004 and 2004-2007 with corresponding response rates of

125 99.8%, 98.7% and 96.7%, respectively.

126 The incident lung cancer cases were defined as a primary tumor with an International Classification of
127 Diseases (ICD)-9 code 162, and were identified through annual record linkage to the Shanghai Cancer
128 Registry and Shanghai Municipal Registry of Vital Statistics. All possible cancer cases were verified
129 through home visits and further review of medical charts by clinical and/or pathological experts.

130 Outcome data through December 31, 2010 for both men and women was used for the present analysis,
131 with median follow-up periods of 6.3 years and 12.2 years for SMHS and SWHS, respectively.

132 *Statistical analysis*

133 Cox proportional hazards regression models with age as time scale were used to calculate age-adjusted
134 and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations
135 of type 2 diabetes with the risk of incident lung cancer. Type 2 diabetes (yes/no) was modeled as a
136 time-varying exposure in the current study, meaning that information on type 2 diabetes reported in
137 questionnaire n , was used to prospectively categorize participants for the periods between completion
138 of questionnaires n and $n + 1$, and the risk person-years was allocated to the corresponding groups, the
139 corresponding method was described elsewhere in detail ⁵.

140 Covariates were selected based on their potential to confound or modify the association between type
141 2 diabetes and lung cancer. All covariates were modeled using baseline values. The covariates
142 included in the multivariate-adjusted models were age (less than 50y, 50-60y, more than 60y), birth
143 cohort (1920s, 1930s, 1940s, 1950s, 1960s), education (illiteracy or elementary school, middle school,
144 high school, graduate school), income (low, low to middle, middle to high, high) (see Table 1), body
145 mass index (BMI; less than 18.5, 18.5-24, 24-28, more than 28, according to Chinese standard ²⁹),
146 occupation [housewife (women only), manual, clerical, and professional], smoking status (never

1
2 147 smoking, ever smoking, current smoking, for men), smoking pack-years (0-10, 10-20, more than 20,
3
4
5 148 for men), ever smoking (yes/no, for women), alcohol drinking(0, 0-1.5, more than 1.5, drink/day, for
6
7 149 men), ever alcohol drinking (yes/no, for women), family history of cancer (yes/no), total energy intake
8
9
10 150 (kcal/day, quartiles), fruit intake (g/day, quartiles), vegetable intake (g/day, quartiles), total physical
11
12 151 activity [PA; standard metabolic equivalents (METs) as MET-hr/day in quartiles; 1 MET-hr=15
13
14 152 minutes of moderate intensity activity]^{30 31}, history of hepatitis/chronic liver disease (yes/no),
15
16
17 153 hormone replacement therapy (HRT; yes/no for women only), menopausal status
18
19
20 154 (pre-/post-menopausal for women only).

21
22
23 155 We also tested for potential interactions of diabetes with age, income, education, occupation, family
24
25 156 history of lung cancer, alcohol drinking, physical activity, and smoking, by comparing the Cox models
26
27
28 157 with and without the interaction terms using a likelihood ratio test. In testing of the proportional
29
30 158 hazard assumption by creating interaction of diabetes and a logarithm of time in the model, we found
31
32
33 159 no violation of proportionality.

34
35
36 160 To investigate the potential effect for over detection bias (i.e. the increased detection around the time
37
38 161 of type 2 diabetes diagnosis), age-adjusted incidence rates by different time intervals of follow-up
39
40 162 (0–1, 1–3, more than 3 years) in diabetes cohort and no-diabetes cohort were calculated for lung
41
42
43 163 cancer, which were directly standardized by the entire cohort population. To examine whether
44
45 164 diabetes treatments affect the risk of lung cancer associated with T2D, a separate analysis that
46
47
48 165 excluded treated diabetes was conducted.

49
50
51
52 166 All data analyses were performed with SAS 9.2 (SAS Institute, Cary, NC), and a two-sided *P* value of
53
54 167 0.05 was considered statistically significant if not specified.

57 168 **Results**

1
2 169 ***Results from the SMHS and SWHS***
3

4
5 170 The distributions of selected baseline characteristics according to type 2 diabetes are shown in Table 1.
6
7
8 171 In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with
9
10 172 type 2 diabetes at baseline or during follow up periods. Compared to men and women without
11
12
13 173 diabetes, patients with type 2 diabetes were older and had higher BMI, greater intake of total energy
14
15 174 and vegetable, but less fruit consumption and alcohol drinking at baseline. In SWHS, less than 2.8%
16
17
18 175 of the women reported ever smoking.
19

20
21 176 **Through December 31, 2010, incident lung cancer case was detected in 492 men and 525 women.** For
22
23 177 men, the age-standardized incidence rates (1/100 000 person-years) of lung cancer were 87.48, 20.73,
24
25
26 178 and 161.92 for 0-1, 1-3, **more than 3** years following the diabetes index date in diabetes cohort,
27
28 179 respectively; 112.97, 119.57, and 141.81 for 0-1, 1-3, **more than 3** years since baseline interview for
29
30
31 180 the cohort without diabetes, respectively. For women, the age-standardized incidence rates (1/100 000
32
33 181 person-years) were 80.53, 19.81, 72.85 for 0-1, 1-3, **more than 3** years following the diabetes index
34
35
36 182 date in diabetes cohort, respectively; and 29.68, 41.43, 69.46 for 0-1, 1-3, **more than 3** years since
37
38
39 183 baseline interview for non-diabetes cohort, respectively.
40

41
42 184 After adjustments for smoking, BMI, alcohol drinking, and other factors, type 2 diabetes was not
43
44 185 associated with the risk of developing lung cancer either in men (HR=0.87, 95%CI: 0.62-1.21) or in
45
46 186 women (HR=0.93, 95%CI: 0.69-1.25) (Table 2). This null association remained when the analysis was
47
48
49 187 restricted to never smokers (Table 3) or after excluding lung cancer cases diagnosed within the first 3
50
51
52 188 years after diabetes diagnosis (Table 2). Results from subgroup analysis by waist to hip ratio, waist
53
54 189 circumference, smoking, and menopausal status (women) did not appreciably alter the main results
55
56
57 190 (Table 3). We did not observe effect modification by age, income, education, occupation, family
58
59
60

1
2 191 history of lung cancer, alcohol drinking, or physical activity. In addition, an additional analysis that
3
4 192 excluded treated diabetes also showed a null association between untreated diabetes and lung cancer
5
6
7 193 (data not shown).
8
9

10 194 Discussion

11
12
13 195 No observational study, to our knowledge, has investigated lung cancer risk in relation to type 2
14
15 196 diabetes in mainland China to date. Findings from our population-based cohort study suggested that
16
17 197 type 2 diabetes is not associated with the risk of incident lung cancer among Chinese adults. This null
18
19 198 association remained regardless of age, income, education, occupation, family history of lung cancer,
20
21 199 alcohol drinking, physical activity, smoking status, menopausal status, and WHR in stratified analysis.
22
23
24 200 Previous epidemiological studies on type 2 diabetes and lung cancer yielded conflicting results,
25
26 201 varying from a positive^{16 32}, null^{17 19-22 24 33-35} to an inverse⁹⁻¹¹ association. Differing study design,
27
28 202 sample size or follow up time, and covariates adjustments may, in part, explain this inconsistency. A
29
30 203 comparative study⁸ and 3 cohort studies⁹⁻¹¹ without adjustments for smoking concluded an inverse
31
32 204 association; two cohort studies that reported a positive association have not adjusted for BMI¹⁶ or
33
34 205 smoking³²; two studies^{25 26} with a null association used case-control design; three studies have a
35
36 206 limited follow up periods (<5y)^{11 21} or sample size (<10,000)¹⁵. Consistent with most pertinent
37
38 207 studies^{17 19-22 24 33-35}, we observed a null association between type 2 diabetes and lung cancer risk
39
40
41 208 overall and among nonsmoking participants.
42
43
44
45
46
47
48

49 209 Although a null association was found between T2D and lung cancer, previous observational studies
50
51 210 have inconsistently shown the increased risk of incident several cancers among individuals with type 2
52
53 211 diabetes, including cancers of liver^{5 6} and pancreas⁷. The potential biologic links between diabetes
54
55 212 and cancer risk included hyperinsulinemia (either endogenous due to insulin resistance or exogenous
56
57
58
59
60

1
2 213 due to administered insulin or insulin secretagogues), hyperglycemia, and/or chronic inflammation³⁶.
3
4
5 214 The hyperinsulinemia may involve in carcinogenesis by its mitogenic effect via the insulin/
6
7 215 insulin-like growth factor (IGF) axis³⁶. On the other hand, hyperglycemia may cause an abnormal
8
9
10 216 energy balance and impair the effect of ascorbic acid on the intracellular metabolism and reduce the
11
12 217 effectiveness of the immune system³⁷, which could favor cancer incidence and progression in diabetic
13
14
15 218 patients. In addition, free fatty acids, interleukin-6, monocyte chemoattractant protein, plasminogen
16
17 219 activator inhibitor-1, adiponectin, leptin, and tumor necrosis factor- α , which were produced by
18
19
20 220 adipose tissue among T2D related obesity, may play an etiologic role in regulating malignant
21
22 221 transformation or cancer progression³⁶.
23
24
25 222 Strengths of our study include the population-based cohort design, large sample size, high response
26
27
28 223 rates of follow ups (over 96% for in-person home visits), and the use of repeated measures of diabetes
29
30
31 224 status. However, several limitations to this study should be noted. As diabetes were self-reported and a
32
33 225 number of patients with diabetes did not know they had the disease³⁸, the misclassification of type 2
34
35
36 226 diabetes cannot be ruled out and could be non-differential, thus led to the underestimation of the true
37
38 227 association. **Nevertheless, we observed a high agreement between self-report data and data from**
39
40 228 **medical records and laboratory test for T2D in a random sample of subjects from our cohorts.** Also,
41
42
43 229 previous validation studies^{39 40} indicated that a self-reported history of diabetes could be reasonably
44
45
46 230 accurate and could provide a useful assessment for broad measures of diabetes in the large-scale
47
48 231 observational study.
49
50
51 232 In addition, the findings from SWHS would have been affected by over-detection bias, given higher
52
53
54 233 incidence rate of lung cancer in the first year following the diabetes index date compared to those
55
56 234 without diabetes regardless of different time intervals of follow-up. However, the results were
57
58
59
60

1
2 235 unchanged in the analysis after excluding lung cancer cases occurred within the first 3 years after
3
4
5 236 diabetes onset. Moreover, this potential increased ascertainment in diabetics is unlikely to occur in
6
7 237 SMHS because of the lower incidence rate of lung cancer in the diabetic cohort within the first year
8
9
10 238 after the diabetes diagnosis.

11
12
13 239 Other limitations to the study include the lack of pharmacologic data on diabetes treatments, including
14
15 240 hypoglycemic agents use and degree of glucose control. However, sensitivity analysis showed a
16
17 241 similarly null association between untreated diabetes and risk of lung cancer, indicating that the
18
19 242 diabetes treatments may not affect our main results. Whereas this finding should be interpreted with
20
21 243 cautions because the information for the history of hypoglycemic drug use were also on the basis of
22
23 244 self-reported data in our study.
24
25
26
27

28
29 245 In summary, our cohort study indicated that type 2 diabetes is not associated with lung cancer risk.
30
31 246 Future research to find other modifiable risk factors for lung cancer should be warranted.
32
33

34 247
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 248 **Acknowledgements** We would like to thank the participants of the Shanghai Men's Health Study and
4
5 249 the Shanghai Women's Health Study for the invaluable contribution to this work.

6
7 250 **Contributions** YBX contributed to the conception and design of the study; YBX, HLL and YTG
8
9
10 251 acquired data; WSY, YY and YBX performed the statistical analysis and the interpretation of results;
11
12 252 WSY wrote the first draft; All authors contributed to the critical review of the manuscript and
13
14 253 approved the final manuscript; The corresponding author (YBX) had full access to all of the data and
15
16 254 the final responsibility for the decision to submit for publication.

17
18
19
20
21 255 **Funding** This work was supported by the US National Institutes of Health (grant number R37
22
23 256 CA070867 and R01 CA82729); the fund of Key Discipline and Specialty Foundation of Shanghai
24
25
26 257 Municipal Commission of Health and Family Planning.

27
28 258 **Competing interests** None. The funding sponsor had no role in the study design, data collection,
29
30
31 259 statistical analysis and result interpretation, as well as in the writing of the report and the decision to
32
33 260 submit for publication. The corresponding author had full access to all data in the study and final
34
35 261 responsibility for the decision to submit for publication.

36
37
38 262 **Study approval** Institutional review board.

39
40
41 263 **Ethics approval** IRBs of Vanderbilt University (USA) and Shanghai Cancer Institute (China).

42
43
44 264

265 **Reference**

- 266 1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;**61**(2):69-90.
- 267 2. Pan XR, Yang WY, Li GW, et al. Prevalence of diabetes and its risk factors in China, 1994. National
268 Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997;**20**(11):1664-9.
- 269 3. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med*
270 2010;**362**(12):1090-101.
- 271 4. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care*
272 2011;**34**(6):1249-57.
- 273 5. Yang WS, Shu XO, Gao J, et al. Prospective evaluation of type 2 diabetes mellitus on the risk of
274 primary liver cancer in Chinese men and women. *Ann Oncol* 2013;**24**(6):1679-85.
- 275 6. Yang WS, Va P, Bray F, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma
276 occurrence and prognosis: a meta-analysis of prospective cohort studies. *PLoS One*
277 2011;**6**(12):e27326.
- 278 7. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of
279 cohort studies. *Eur J Cancer* 2011;**47**(13):1928-37.
- 280 8. Armstrong B, Lea AJ, Adelstein AM, et al. Cancer mortality and saccharin consumption in diabetics.
281 *Br J Prev Soc Med* 1976;**30**(3):151-7.
- 282 9. Atchison EA, Gridley G, Carreon JD, et al. Risk of cancer in a large cohort of U.S. veterans with
283 diabetes. *Int J Cancer* 2011;**128**(3):635-43.
- 284 10. Lo SF, Chang SN, Muo CH, et al. Modest increase in risk of specific types of cancer types in type
285 2 diabetes mellitus patients. *Int J Cancer* 2013;**132**(1):182-8.
- 286 11. Ogunleye AA, Ogston SA, Morris AD, et al. A cohort study of the risk of cancer associated with

- 1
2 287 type 2 diabetes. *Br J Cancer* 2009;**101**(7):1199-201.
- 3
4
5 288 12. Emerging Risk Factors C, Seshasai SR, Kaptoge S, et al. Diabetes mellitus, fasting glucose, and
6
7 289 risk of cause-specific death. *N Engl J Med* 2011;**364**(9):829-41.
- 8
9
10 290 13. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese
11
12 291 men and women. *Eur J Cancer Prev* 2007;**16**(1):83-9.
- 13
14
15 292 14. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and
16
17 293 insulin effects. *Diabetologia* 2012;**55**(4):948-58.
- 18
19
20 294 15. Luo J, Chlebowski R, Wactawski-Wende J, et al. Diabetes and lung cancer among postmenopausal
21
22 295 women. *Diabetes Care* 2012;**35**(7):1485-91.
- 23
24
25 296 16. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and
26
27 297 women. *JAMA* 2005;**293**(2):194-202.
- 28
29
30 298 17. Coughlin SS, Calle EE, Teras LR, et al. Diabetes mellitus as a predictor of cancer mortality in a
31
32 299 large cohort of US adults. *Am J Epidemiol* 2004;**159**(12):1160-7.
- 33
34
35 300 18. Saydah SH, Loria CM, Eberhardt MS, et al. Abnormal glucose tolerance and the risk of cancer
36
37 301 death in the United States. *Am J Epidemiol* 2003;**157**(12):1092-100.
- 38
39
40 302 19. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer: results from a
41
42 303 large-scale population-based cohort study in Japan. *Arch Intern Med* 2006;**166**(17):1871-7.
- 43
44
45 304 20. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I.
46
47 305 Follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiol*
48
49 306 *Biomarkers Prev* 1995;**4**(8):807-11.
- 50
51
52 307 21. Hall GC, Roberts CM, Boulis M, et al. Diabetes and the risk of lung cancer. *Diabetes Care*
53
54 308 2005;**28**(3):590-4.
- 55
56
57 309 22. Khan M, Mori M, Fujino Y, et al. Site-specific cancer risk due to diabetes mellitus history:

- 1
2 310 evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev*
3
4 311 2006;7(2):253-9.
5
6
7 312 23. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than
8
9 313 140,000 adults in Austria. *Diabetologia* 2006;49(5):945-52.
10
11 314 24. Stattin P, Bjor O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes*
12
13 315 *Care* 2007;30(3):561-7.
14
15
16 316 25. Rousseau MC, Parent ME, Pollak MN, et al. Diabetes mellitus and cancer risk in a
17
18 317 population-based case-control study among men from Montreal, Canada. *Int J Cancer*
19
20 318 2006;118(8):2105-9.
21
22
23 319 26. O'Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control
24
25 320 study. *J Chronic Dis* 1985;38(5):435-41.
26
27
28 321 27. Villegas R, Yang G, Liu D, et al. Validity and reproducibility of the food-frequency questionnaire
29
30 322 used in the Shanghai men's health study. *Br J Nutr* 2007;97(5):993-1000.
31
32
33 323 28. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design,
34
35 324 and baseline characteristics. *Am J Epidemiol* 2005;162(11):1123-31.
36
37
38 325 29. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive
39
40 326 values of body mass index and waist circumference for risk factors of certain related diseases
41
42 327 in Chinese adults--study on optimal cut-off points of body mass index and waist circumference
43
44 328 in Chinese adults. *Biomed Environ Sci* 2002;15(1):83-96.
45
46
47 329 30. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of
48
49 330 activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32(9 Suppl):S498-504.
50
51
52 331 31. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of
53
54 332 energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25(1):71-80.
55
56
57
58
59
60

- 1
2 333 32. Chodick G, Heymann AD, Rosenmann L, et al. Diabetes and risk of incident cancer: a large
3
4 334 population-based cohort study in Israel. *Cancer Causes Control* 2010;**21**(6):879-87.
5
6
7 335 33. Ehrlich SF, Quesenberry CP, Jr., Van Den Eeden SK, et al. Patients diagnosed with diabetes are at
8
9 336 increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and
10
11 337 pneumonia but not lung cancer. *Diabetes Care* 2010;**33**(1):55-60.
12
13
14 338 34. Wotton CJ, Yeates DG, Goldacre MJ. Cancer in patients admitted to hospital with diabetes mellitus
15
16 339 aged 30 years and over: record linkage studies. *Diabetologia* 2011;**54**(3):527-34.
17
18
19 340 35. Yeh HC, Platz EA, Wang NY, et al. A prospective study of the associations between treated
20
21 341 diabetes and cancer outcomes. *Diabetes Care* 2012;**35**(1):113-8.
22
23
24 342 36. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes*
25
26 343 *Care* 2010;**33**(7):1674-85.
27
28
29 344 37. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. *Endocr Relat Cancer*
30
31 345 2009;**16**(4):1103-23.
32
33
34 346 38. Li R, Lu W, Jiang QW, et al. Increasing prevalence of type 2 diabetes in Chinese adults in
35
36 347 Shanghai. *Diabetes Care* 2012;**35**(5):1028-30.
37
38
39 348 39. Martin LM, Leff M, Calonge N, et al. Validation of self-reported chronic conditions and health
40
41 349 services in a managed care population. *Am J Prev Med* 2000;**18**(3):215-8.
42
43
44 350 40. Wu SC, Li CY, Ke DS. The agreement between self-reporting and clinical diagnosis for selected
45
46 351 medical conditions among the elderly in Taiwan. *Public Health* 2000;**114**(2):137-42.
47
48
49 352
50
51
52 353
53
54
55
56
57
58
59
60

Type 2 diabetes and lung cancer

Table 1 Characteristics of study participants according to type 2 diabetes status in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)¹

	Men		Women	
	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes
Number of subjects	55311	4599	66,823	6291
Age at baseline (y)	54.89 (9.63)	60.48 (9.61)	51.94 (8.91)	58.51 (8.34)
Education level (%)				
Illiteracy or elementary school	6.27	11.33	19.28	43.18
Middle school	33.51	33.57	37.95	29.27
High school	36.69	29.53	28.85	18.41
Graduate school/College	23.52	25.57	13.92	9.14
Income (%) ²				
Low	12.86	9.24	15.58	21.43
Low-middle	77.45	80.82	38.08	39.88
Middle-high	8.93	9.26	28.47	24.34
High	0.76	0.68	17.87	14.35
Occupation (%)				
Housewife	-	-	0.34	0.64
Professional	25.79	31.92	29.98	22.78
Clerical	21.92	22.53	20.81	20.32
Manual worker	52.29	45.55	49.87	56.26
BMI kg/m ²	23.64 (3.07)	24.61 (3.04)	23.82 (3.33)	26.00 (3.76)
BMI (%)				
Less than 18.5	4.49	1.48	3.58	1.30
18.5-24.0	50.79	43.23	51.82	29.08
24.0-28.0	37.01	41.47	33.83	42.39
Great than 28	7.71	13.83	10.77	27.23
Smoking status (%)				
Never smokers	29.69	38.16	97.47	95.25
Former smokers	10.29	17.33		
Current smokers	60.02	44.51	2.59 ³	4.75 ³
Physical activity (MET hours/week)	59.56 (34.03)	61.04 (35.83)	107.00 (45.30)	102.50 (43.31)
Ever alcohol intake (%)	34.82	29.03	2.29	1.87
Total energy intake (Kcal/day)	8029.80 (2029.10)	7481.00 (1929.50)	7033.90 (1681.10)	6845.10 (1842.40)
Fruit intake (g/day)	155.10 (125.00)	98.58 (110.50)	271.90 (178.30)	187.90 (175.30)
Vegetable intake (g/day)	341.20 (190.10)	373.20 (218.40)	295.70 (168.70)	305.70 (188.70)
Family history of cancer (%)	28.27	30.03	26.48	26.61
Post-menopausal (%)	-	-	46.27	76.58
HRT use (%)	-	-	2.07	2.10

¹ Abbreviations: BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-hr=15 minutes of moderate intensity activity); HRT, hormone replacement therapy. Continuous variables are presented as the mean (the standard deviation).

² Low: less than 10,000 Yuan per family per year for women and less than 1000 Yuan per person per month for men; Low to middle: 10,000 - 19,999 Yuan per family per year for women and 1000-3000 Yuan per person per month for men; Middle to high: 20,000-29,999 Yuan per family per year for women and 3000-5000 Yuan per person per month for men; High: greater

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

than 30,000 Yuan per family per year for women and more than 5000 Yuan per person per month for men.

³ Due to small number of smokers among women, the number of current and former smokers was combined.

For peer review only

Type 2 diabetes and lung cancer

Table 2 Hazard ratios for the association between type 2 diabetes and lung cancer risk in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)

	No type 2 diabetes		Type 2 diabetes		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) ¹
Men					
Entire cohort	450/354,902	1.00(referent)	42/28,825	0.80(0.58-1.10)	0.87(0.62-1.21)
Sensitivity analysis ²	260/354,604	1.00(referent)	28/28,805	0.94(0.64-1.39)	1.10(0.73-1.64)
Women					
Entire cohort	469/801,158	1.00(referent)	56/72,600	0.88(0.66-1.18)	0.93(0.69-1.25)
Sensitivity analysis ²	396/801,041	1.00(referent)	52/72,596	0.93(0.69-1.26)	0.99(0.72-1.34)

¹ Adjusted for age, birth cohort, education, income, body mass index, occupation, smoking status, smoking pack years (men only), alcohol drinking, family history of lung cancer, total energy intake, fruit intake, vegetable intake, total physical activity, hormone replacement therapy (women only), menopausal status (women only).

² Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Type 2 diabetes and lung cancer

Table 3 Hazard ratios for the association between type 2 diabetes and lung cancer risk, stratified by waist to hip ratio, waist circumference, smoking, and menopausal status (women) in the Shanghai Men's Health Study (2002-2010) and the Shanghai Women's Health Study (1997-2010)¹

	No type 2 diabetes		Type 2 diabetes	
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	HR (95%CI) ¹
Men				
Waist to hip ratio ²				
1 st tertile	187/122,101	1.00(referent)	7/5808	0.59(0.27-1.28)
2 nd tertile	129/121,267	1.00(referent)	10/9063	0.67(0.35-1.30)
3 rd tertile	134/111,533	1.00(referent)	25/13,954	1.13(0.71-1.78)
Waist circumference (cm) ³				
Less than 85	163/93,856	1.00(referent)	4/4254	0.38(0.14-1.04)
Greater than 85	287/261,046	1.00(referent)	38/24,571	1.02(0.71-1.46)
Smoking				
Smoking status				
never smoker	53/106,860	1.00(referent)	10/11,199	1.46(0.71-3.02)
former smoker	76/36,466	1.00(referent)	13/4811	0.97(0.52-1.80)
current smoker	321/211,575	1.00(referent)	19/12,815	0.67(0.41-1.10)
Smoking pack years				
0-10	80/147,829	1.00(referent)	11/14,143	1.06(0.54-2.06)
10-20	55/70,068	1.00(referent)	5/4313	0.93(0.36-2.42)
Greater than 20	315/137,004	1.00(referent)	26/10,369	0.78(0.51-1.19)
Women				
Waist to hip ratio ⁴				
1 st tertile	133/282,622	1.00(referent)	2/8367	0.44(0.11-1.80)
2 nd tertile	139/277,675	1.00(referent)	24/20,108	1.37(0.80-2.34)
3 rd tertile	197/240,861	1.00(referent)	30/44,126	0.63(0.40-1.01)
Waist circumference (cm) ⁵				
Less than 80	245/502,838	1.00(referent)	15/20,482	1.01(0.56-1.82)
More than 80	224/298,320	1.00(referent)	41/52,119	0.74(0.49-1.13)
Smoking status ⁶				
never smoker	428/781,407	1.00(referent)	50/69,261	0.98(0.72-1.34)
former and current smoker	41/19,751	1.00(referent)	6/3339	0.53(0.21-1.39)
Menopausal status				
Yes	365/365,579	1.00(referent)	49/54,772	0.84(0.61-1.50)
No	104/435,575	1.00(referent)	7/17,828	2.12(0.96-4.67)

¹ The adjusted covariates are as indicated in Table 1.² 1st tertile: <0.878; 2nd tertile: 0.878-0.924; 3rd tertile: ≥0.924.³ A waist circumference ≥ 85cm for men was defined as overweight and central adiposity.⁴ 1st tertile: <0.785; 2nd tertile: 0.785-0.831; 3rd tertile: ≥0.831.

⁵ A waist circumference ≥ 80 cm for women was defined as overweight and central adiposity.

⁶ Due to limited number of former smokers among women, the former and current smokers were combined.

For peer review only

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

	Page	Recommendation
Title and abstract	1-3	(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
Introduction		
Background/rationale	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
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
Variables	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-7	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
Bias	8	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	6-9	(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
Results		
Participants	6-7	(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
Descriptive data	9	(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)
Outcome data	9	Report numbers of outcome events or summary measures over time
Main results	9	(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
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	10	Summarise key results with reference to study objectives
Limitations	11-12	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	10-12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	12	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	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

*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>.