

## ONLINE APPENDIX

**Supplementary Table 1. Univariable hazard ratios of metformin usage for cancer after excluding patients with different durations of drug usage prior to enrolment**

Number of years of metformin usage before enrolment	Remaining sample size†	Hazard ratio	95% CI	P value
No exclusion	6103	0.54	0.42 to 0.69	<.0001
0 (exclusion of users at enrolment)	3086	0.38	0.27 to 0.54	<.0001
0.5	2776	0.38	0.26 to 0.55	<.0001
1.0	2727	0.37	0.26 to 0.54	<.0001
1.5	2695	0.37	0.26 to 0.54	<.0001
2.0	2675	0.37	0.26 to 0.54	<.0001
2.5	2658	0.37	0.25 to 0.54	<.0001
3.0	2645	0.37	0.25 to 0.54	<.0001
4.0	2630	0.37	0.25 to 0.54	<.0001
5.0	2622	0.37	0.25 to 0.54	<.0001
6.0	2618	0.37	0.25 to 0.54	<.0001

Abbreviations: 95%CI, 95% confidence interval;

†, Number of remaining patients after excluding those who used methformin during the period before enrolment.

**Supplementary Table 2.. Sensitivity analysis of hazard ratios of combinations of low HDL-C and metformin use for cancer risk in Type 2 diabetes**

<b>Biological Interaction models</b>	<b>Hazard ratio</b>	<b>95% CI</b>	<b>P value</b>
<b>Sensitivity analysis one †,‡</b>			
HDL-C <1.0 mmol/L plus nonuse of metformin	4.40	1.69 to 11.40	.0023
HDL-C ≥1.0 mmol/L plus nonuse of metformin	1.82	0.98 to 3.38	.0602
HDL-C < 1.0 mmol/L plus use of metformin	1.76	0.63 to 4.93	.2824
HDL-C ≥1.0 mmol/L plus use of metformin		Reference	
<b>Sensitivity analysis two †,‡</b>			
HDL-C <1.0 mmol/L plus nonuse of metformin	7.20	2.73 to 18.98	<.0001
HDL-C ≥1.0 mmol/L plus nonuse of metformin	2.00	0.97 to 4.13	.0608
HDL-C < 1.0 mmol/L plus use of metformin	3.35	1.05 to 10.74	.0415
HDL-C ≥1.0 mmol/L plus use of metformin		Reference	
<b>Sensitivity analysis three †,‡</b>			
HDL-C <1.0 mmol/L plus nonuse of metformin	2.91	1.82 to 4.67	<.0001
HDL-C ≥1.0 mmol/L plus nonuse of metformin	1.53	1.53 to 2.07	.0062
HDL-C < 1.0 mmol/L plus use of metformin	1.03	0.67 to 1.57	.9010
HDL-C ≥1.0 mmol/L plus use of metformin		Reference	
<b>Sensitivity analysis four (not adjusted for covariate)</b>			
HDL-C <1.0 mmol/L plus nonuse of metformin	4.37	2.66 to 7.19	<.0001
HDL-C ≥1.0 mmol/L plus nonuse of metformin	2.19	1.45 to 3.31	.0002
HDL-C < 1.0 mmol/L plus use of metformin	1.32	0.71 to 2.45	.3858
HDL-C ≥1.0 mmol/L plus use of metformin		Reference	

Abbreviations: 95%CI, 95% confidence interval; HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers;

Sensitivity analysis one was applied to patients who were followed for 2.5 years and more (n=2170); Sensitivity analysis two was applied to patients who were enrolled after 1 July 1998 (n=1707); Sensitivity analysis three was applied to 3445 patients who used metformin during 2.5 years before enrolment and 2658 patients who did not use the drug during that period; Sensitivity analysis four was applied to 2996 patients who did not have missing values in HDL-C.

†, Adjusted for age, sex, employment status, smoking status, alcohol intake, duration of diabetes BMI (BMI ≥27.6 or < 24.0 kg/m<sup>2</sup>), HbA<sub>1c</sub>, SBP, LDL-C related risk indicators (LDL-C ≥3.8 mmol/L and LDL-C<2.8 mmol/L plus albuminuria), HDL-C ≥ 1.30 mmol/L and the non-linear association of triglyceride with cancer at enrolment, and use of statins, fibrates, other lipid lowering drugs, ACEIs/ARBs and insulin during follow-up;

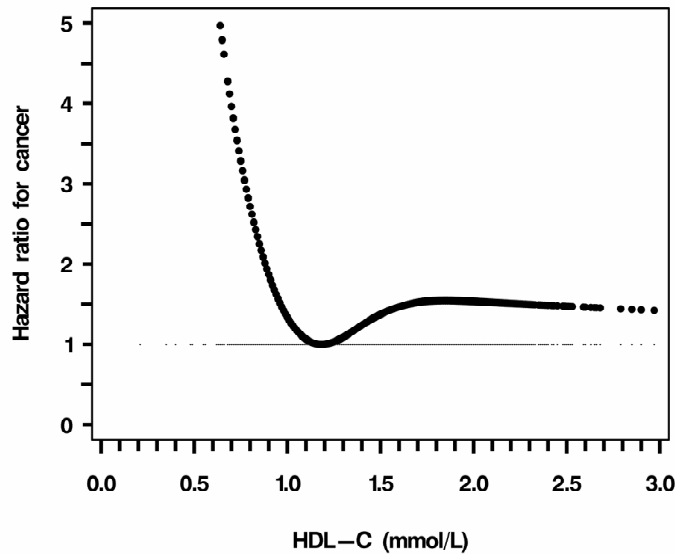
‡, Stratified Cox model analyses on deciles of the propensity score of metformin use were included to control for likelihood of starting metformin therapy during follow-up.

**Supplementary Table 3. Measures for estimation of biological interaction between low HDL cholesterol and nonuse of metformin for the risk of cancer in Type 2 diabetes**

Measures of biological interaction	Estimate	95% confidence interval	P value
<b>Sensitivity analysis one †,‡</b>			
RERI	1.82	-1.88 to 5.52	.7779
AP	0.41	-0.15 to 0.98	.4502
S	2.16	0.52 to 8.98	.6215
<b>Sensitivity analysis two †,‡</b>			
RERI	2.85	-3.03 to 8.72	.3421
AP	0.40	-0.19 to 0.98	.1864
S	1.85	0.55 to 6.21	.4063
<b>Sensitivity analysis three †,‡</b>			
RERI	1.36	0.05 to 2.66	.0414
AP	0.47	0.19 to 0.75	.0011
S	3.44	1.03 to 11.48	.4021
<b>Sensitivity analysis four (not adjusted for covariate)</b>			
RERI	1.86	0.00 to 3.73	.0495
AP	0.43	0.13 to 0.73	.0053
S	2.24	0.98 to 5.11	.1262

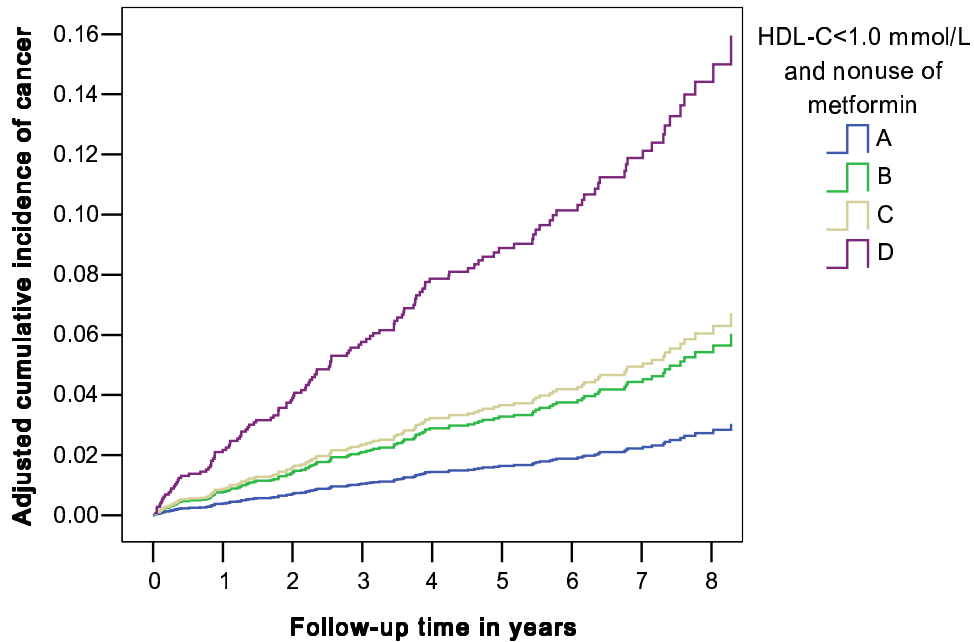
Notes are the same as those in Supplementary table 2.

**Supplementary Figure 1. Hazard ratios of HDL-C for cancer in Type 2 diabetes using spline Cox model analysis.**



The curve was adjusted for age, sex, employment status, smoking status, drinking status, duration of diabetes, BMI ( $\geq 27.6$  or  $< 24.0$  kg/m<sup>2</sup>), HbA<sub>1c</sub>, SBP, LDL-C related risk indicators (LDL-C  $\geq 3.8$  mmol/L and LDL-C  $< 2.8$  mmol/L plus albuminuria), and the non-linear association of triglyceride with cancer at enrolment and use of statins, fibrates, other lipid lowering drugs, ACEIs/ARBs, metformin and insulin during follow-up.

**Supplementary Figure 2. Cumulative incidence of cancer stratified by a combination of HDL-C <1.0 mmol/L and non-use of metformin during follow-up period**



A, HDL-C  $\geq 1.0$  mmol/L plus use of metformin during follow-up period (the last curve from the top). B, HDL-C < 1.0 mmol/L plus use of metformin during follow-up period (the third curve from the top); C, HDL-C  $\geq 1.0$  mmol/L plus non-use of metformin during follow-up period (the second curve from the top); and D, HDL-C < 1.0 mmol/L plus non-use of metformin during follow-up period (the first curve from the top); The model was adjusted for LDL-C related risk indicators (LDL-C  $\geq 3.8$  mmol/L and LDL-C < 2.8 mmol/L plus albuminuria), HDL-C  $\geq 1.30$  mmol/L and the non-linear association of triglyceride with cancer, age, sex, employment status, smoking status, drinking status, duration of diabetes, BMI ( $\geq 27.6$  or  $< 24.0$  kg/m<sup>2</sup>), HbA<sub>1c</sub>, and SBP at enrolment, and use of statins, fibrates, other lipid lowering drugs, ACEIs/ARBs and insulin during follow-up, as well as probability of starting metformin during follow-up (used as a covariate). P was derived from Cox model, P < 0.0001 for D vs. A; P = .0007 for B vs. A; and P = .0708 for C vs. A