

**Metformin Treatment and Cancer Risk: Cox Regression Analysis With
Time-Dependent Covariates of 320,000 Persons With Incident Diabetes
Mellitus**

Rachel Dankner, Nirit Agay, Liraz Olmer, Havi Murad, Lital Keinan Boker, Ran
D. Balicer, and Laurence S. Freedman

Table of contents:

Web Appendix

Web Tables 1–5

Web Appendix

Development of the Cox Model for Incorporating Weighted Cumulative Exposure

As explained in the Methods section of the main text, we made a simplifying assumption that the weighted cumulative exposure was represented by:

$$WCE(t) = w_1 \sum_{u=1}^4 D(t-u) + w_2 \sum_{u=5}^{16} D(t-u) + w_3 \sum_{u=17}^{28} D(t-u) + w_4 \sum_{u=29}^{40} D(t-u),$$

where t represents the current quarter, $D(t)$ is the average dose taken in quarter t , and the w 's are unknown weights.

Furthermore, we assumed the following Cox model:

$$\lambda(t) = \lambda_0(t) \exp \{ \beta_w WCE(t) + \beta_c C \} \quad (A1)$$

where $\lambda(t)$ is the individual's hazard rate at time t for the cancer of interest, $\lambda_0(t)$ is the baseline hazard rate, β_w is the coefficient of $WCE(t)$, C are the baseline confounders, and β_c are their coefficients. Substituting the above expression for $WCE(t)$ into the model (A1), we obtain:

$$\lambda(t) = \lambda_0(t) \exp \left\{ \beta_w \left[w_1 \sum_{u=1}^4 D(t-u) + w_2 \sum_{u=5}^{16} D(t-u) + w_3 \sum_{u=17}^{28} D(t-u) + w_4 \sum_{u=29}^{40} D(t-u) \right] + \beta_c C \right\}$$

We now write $D_1(t) = \sum_{u=1}^4 D(t-u) / 4$, the mean dose taken in the year

previous to quarter t . Similarly, we write $D_2(t) = \sum_{u=5}^{16} D(t-u) / 12$,

$$D_3(t) = \sum_{u=17}^{28} D(t-u)/12 \text{ and } D_4(t) = \sum_{u=29}^{40} D(t-u)/12, \text{ the mean doses over the}$$

years 1-4, 5-7 and 8-10 previous to t. This yields the model:

$$\lambda(t) = \lambda_0(t) \exp\{\beta_w [4w_1D_1(t) + 12w_2D_2(t) + 12w_3D_3(t) + 12w_4D_4(t)] + \beta_C C\}.$$

Finally, we set $\beta_1 = 4\beta_w w_1, \beta_2 = 12\beta_w w_2, \beta_3 = 12\beta_w w_3,$ and $\beta_4 = 12\beta_w w_4$ to

give us the Cox model

$$\lambda(t) = \lambda_0(t) \exp\{\beta_1 D_1(t) + \beta_2 D_2(t) + \beta_3 D_3(t) + \beta_4 D_4(t) + \beta_C C\},$$

as written in the main text. The variables $D_1(t), D_2(t), D_3(t)$ and $D_4(t)$ can be readily calculated from the mean doses in each quarter, according to the formulas given above.

Web Table 1. Regression Coefficient Estimates for the Cox Model for Assessing Association Between Metformin Exposure and All-Sites Cancer (Excluding Prostate and Pancreatic Cancer) During 2004–2012 in Israeli Individuals with Diabetes, Controlling for All Other Glucose-Lowering Medications, and Adjusting for Confounding Variables

Variable (Reference Group)	Category (for Categorical Variables) or Time Period (for Drug Variables)	Estimated Coefficient	Standard Error	P Value (2-Sided)
Age (vs. <55 years)	55–59 years	2.25	0.50	<0.001
	60–64 years	2.50	0.50	<0.001
	65–69 years	2.71	0.50	<0.001
	70–74 years	2.84	0.50	<0.001
	75–79 years	2.90	0.50	<0.001
	80–84 years	3.00	0.50	<0.001
	≥85 years	2.95	0.50	<0.001
Sex (vs. male)	Female	-0.004	0.05	0.82
SES (vs. low)	High	-0.039	0.028	0.16
	Medium	-0.047	0.021	0.03
	Missing	-0.026	0.057	0.65
Ethnicity/country of origin (vs. European-American Jew)	Israel Arab	-0.42	0.03	<0.001
	Ethiopian Jew	-0.86	0.12	<0.001
	Israel Jew	-0.16	0.03	<0.001
	Asian-African Jew	-0.24	0.02	<0.001
	Yemeni Jew	-0.35	0.05	<0.001
Insulin	Previous year	0.11	0.08	0.19
	Previous 1–4 years	0.00	0.16	0.99
	Previous 5–7 years	-0.15	0.28	0.59
	Previous 8–10 years	0.38	0.61	0.54
Metformin (with or without DPP4i)	Previous year	0.01	0.05	0.87
	Previous 1–4 years	-0.05	0.08	0.57
	Previous 5–7 years	0.03	0.11	0.79
	Previous 8–10 years	0.39	0.23	0.09
Insulin secretagogues ^a and incretin mimetics ^b	Previous year	0.05	0.05	0.34
	Previous 1–4 years	-0.02	0.09	0.83
	Previous 5–7 years	0.11	0.14	0.43
	Previous 8–10 years	-0.29	0.36	0.43
Alpha-glucosidase inhibitor	Previous year	0.40	0.39	0.30
	Previous 1–4 years	-1.14	0.68	0.09
	Previous 5–7 years	1.45	0.83	0.08
	Previous 8–10 years	-5.72	3.56	0.10
Rosiglitazone	Previous year	-0.36	0.30	0.22
	Previous 1–4 years	0.34	0.39	0.38
	Previous 5–7 years	-0.35	0.70	0.62
	Previous 8–10 years	-4.41	5.57	0.43

DPP4i, dipeptidyl peptidase-4 inhibitors.

^a Sulfonylureas and meglitinides.

^b Dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists.

Web Table 2. Regression Coefficient Estimates for the Cox Model for Assessing Association Between Metformin Exposure and Colon Cancer (Excluding Prostate and Pancreatic Cancer) During 2004–2012 in Israeli Individuals with Diabetes, Controlling for All Other Glucose-Lowering Medications, and Adjusting for Confounding Variables

Variable (Reference Group)	Category (for Categorical Variables) or Time-Period (for Drug Variables)	Estimated Coefficient	Standard Error	P Value (2-Sided)
Age (vs. <50 years)	50–59 years	0.99	0.11	<0.001
	60–69 years	1.75	0.10	<0.001
	70–79 years	2.16	0.10	<0.001
	≥80 years	2.31	0.11	<0.001
Sex (vs. male)	Female	-0.39	0.04	<0.001
SES (vs. low)	High	-0.11	0.07	0.09
	Medium	-0.05	0.05	0.34
	Missing	-0.04	0.14	0.78
Ethnicity/country of origin (vs. European-American Jew)	Israel Arab	-0.40	0.08	<0.001
	Ethiopian Jew	-1.30	0.34	0.001
	Israel Jew	-0.54	0.07	<0.001
	Asian–African Jew	-0.30	0.05	<0.001
	Yemeni Jew	-0.24	0.11	0.02
Insulin	Previous year	-0.14	0.24	0.56
	Previous 1–4 years	0.24	0.43	0.58
	Previous 5–7 years	-0.35	0.92	0.70
	Previous 8–10 years	13.0	13.2	0.33
Metformin (with or without DPP4i)	Previous year	0.08	0.12	0.52
	Previous 1–4 years	0.13	0.19	0.50
	Previous 5–7 years	-0.08	0.26	0.76
	Previous 8–10 years	-0.70	0.68	0.30
Insulin secretagogues ^a and incretin mimetics ^b	Previous year	-0.15	0.13	0.27
	Previous 1–4 years	0.54	0.22	0.014
	Previous 5–7 years	-0.58	0.37	0.12
	Previous 8–10 years	1.11	0.81	0.17
Alpha-glucosidase inhibitor	Previous year	0.02	1.17	0.99
	Previous 1–4 years	-2.77	2.48	0.27
	Previous 5–7 years	-3.06	4.62	0.51
	Previous 8–10 years	-1.02	9.61	0.92
Rosiglitazone	Previous year	-0.26	0.73	0.72
	Previous 1–4 years	0.54	1.06	0.61
	Previous 5–7 years	-6.49	4.77	0.17
	Previous 8–10 years	5.29	3.34	0.11

DPP4i, dipeptidyl peptidase-4 inhibitors.

^a Sulfonylureas and meglitinides.

^b Dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists.

Web Table 3. Regression Coefficient Estimates for the Cox Model for Assessing Association Between Metformin Exposure and Breast Cancer (Excluding Prostate and Pancreatic Cancer) During 2004–2012 in Israeli Individuals with Diabetes, Controlling for All Other Glucose-Lowering Medications, and Adjusting for Confounding Variables

Variable (Reference Group)	Category (for Categorical Variables) or Time-Period (for Drug Variables)	Estimated Coefficient	Standard Error	P Value (2-Sided)
Age (vs. <50 years)	50–59 years	0.82	0.08	<0.001
	60–69 years	1.06	0.08	<0.001
	70–79 years	0.86	0.08	<0.001
	≥80 years	0.95	0.11	<0.001
SES (vs. low)	High	0.15	0.07	0.03
	Medium	0.06	0.05	0.27
	Missing	0.11	0.14	0.46
Ethnicity/country of origin (vs. European-American Jew)	Israel Arab	-0.51	0.09	<0.001
	Ethiopian Jew	-1.14	0.36	0.0014
	Israel Jew	0.02	0.07	0.74
	Asian–African Jew	-0.08	0.06	0.17
	Yemeni Jew	-0.06	0.12	0.60
Parity (vs. 0 children)	1	0.01	0.07	0.90
	2–3	0.04	0.07	0.51
	4+	-0.18	0.08	0.03
Insulin	Previous year	0.13	0.22	0.55
	Previous 1–4 years	-0.09	0.40	0.82
	Previous 5–7 years	0.33	0.69	0.64
	Previous 8–10 years	1.25	0.66	0.06
Metformin (with or without DPP4i)	Previous year	0.21	0.13	0.10
	Previous 1–4 years	-0.05	0.20	0.78
	Previous 5–7 years	-0.07	0.27	0.80
	Previous 8–10 years	0.19	0.59	0.74
Insulin secretagogues ^a and incretin mimetics ^b	Previous year	0.18	0.13	0.17
	Previous 1–4 years	-0.29	0.24	0.23
	Previous 5–7 years	0.27	0.36	0.46
	Previous 8–10 years	-1.34	1.11	0.23
Alpha-glucosidase inhibitor	Previous year	0.88	0.81	0.27
	Previous 1–4 years	-1.71	1.43	0.23
	Previous 5–7 years	4.26	1.26	0.0007
	Previous 8–10 years	-41.9	30.1	0.16
Rosiglitazone	Previous year	0.05	0.84	0.95
	Previous 1–4 years	-1.91	1.45	0.19
	Previous 5–7 years	0.70	1.95	0.72
	Previous 8–10 years	11.9	27.8	0.67

DPP4i, dipeptidyl peptidase-4 inhibitors.

^a Sulfonylureas and meglitinides.

^b Dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists.

Web Table 4. Regression Coefficient Estimates for the Cox Model for Assessing Association Between Metformin Exposure and Lung Cancer (Excluding Prostate and Pancreatic Cancer) During 2004–2012 in Israeli Individuals with Diabetes, Controlling for All Other Glucose-Lowering Medications, and Adjusting for Confounding Variables

Variable (Reference Group)	Category (for Categorical Variables) or Time-Period (for Drug Variables)	Estimated Coefficient	Standard Error	P Value (2-Sided)
Age (vs. <50 years)	50–59 years	1.49	0.15	<0.001
	60–69 years	2.21	0.14	<0.001
	70–79 years	2.50	0.15	<0.001
	≥80 years	2.58	0.17	<0.001
Sex (vs. male)	Female	-0.39	0.06	<0.001
SES (vs. low)	High	-0.26	0.09	0.002
	Medium	-0.17	0.07	0.011
	Missing	-0.43	0.20	0.031
Ethnicity/country of origin (vs. European-American Jew)	Israel Arab	-0.19	0.09	0.047
	Ethiopian Jew	-1.32	0.58	0.022
	Israel Jew	-0.23	0.09	0.009
	Asian–African Jew	-0.28	0.07	<0.001
	Yemenite Jew	-0.44	0.16	0.006
Smoking (vs. never smoked or missing)	Current or former smoker	1.22	0.06	<0.0001
Insulin	Previous year	0.18	0.22	0.40
	Previous 1–4 years	0.03	0.40	0.94
	Previous 5–7 years	0.26	0.69	0.70
	Previous 8–10 years	-2.17	3.82	0.57
Metformin (with or without DPP4i)	Previous year	-0.07	0.15	0.65
	Previous 1–4 years	-0.16	0.25	0.52
	Previous 5–7 years	0.18	0.32	0.57
	Previous 8–10 years	0.84	0.65	0.20
Insulin secretagogues ^a and incretin mimetics ^b	Previous year	-0.03	0.17	0.86
	Previous 1–4 years	0.03	0.28	0.92
	Previous 5–7 years	0.25	0.42	0.56
	Previous 8–10 years	-1.23	1.17	0.29
Alpha-glucosidase inhibitor	Previous year	0.77	1.07	0.47
	Previous 1–4 years	-0.29	1.92	0.88
	Previous 5–7 years	-2.74	3.80	0.47
	Previous 8–10 years	0.44	7.77	0.96
Rosiglitazone	Previous year	-1.21	0.87	0.17
	Previous 1–4 years	2.36	0.81	0.004
	Previous 5–7 years	-1.86	2.07	0.37
	Previous 8–10 years	-	-	-

DPP4i, dipeptidyl peptidase-4 inhibitors.

^a Sulfonylureas and meglitinides.

^b Dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists.

Web Table 5. Regression Coefficient Estimates for the Cox Model for Assessing Association Between Metformin Exposure and Bladder Cancer (Excluding Prostate and Pancreatic Cancer) During 2004–2012 in Israeli Individuals with Diabetes, Controlling for All Other Glucose-Lowering Medications, and Adjusting for Confounding Variables

Variable (Reference Group)	Category (for Categorical Variables) or Time-Period (for Drug Variables)	Estimated Coefficient	Standard Error	P Value (2-Sided)
Age (vs. <50 years)	50–59 years	1.35	0.21	<0.001
	60–69 years	2.14	0.20	<0.001
	70–79 years	2.61	0.20	<0.001
	≥80 years	3.03	0.22	<0.001
Sex (vs. male)	Female	-1.48	0.10	<0.001
SES (vs. low)	High	-0.02	0.11	0.84
	Medium	-0.14	0.09	0.10
	Missing	0.15	0.20	0.47
Ethnicity/country of origin (vs. European-American Jew)	Israel Arab	-0.14	0.13	0.28
	Ethiopian Jew	-2.01	1.00	0.045
	Israel Jew	0.06	0.11	0.59
	Asian–African Jew	-0.03	0.09	0.74
	Yemenite Jew	-0.48	0.22	0.029
Smoking (vs. never smoked or missing)	Current or former smoker	0.70	0.08	<0.001
Insulin	Previous year	0.32	0.21	0.13
	Previous 1–4 years	0.23	0.38	0.55
	Previous 5–7 years	-1.82	1.42	0.20
	Previous 8–10 years	2.08	1.26	0.10
Metformin (with or without DPP4i)	Previous year	-0.02	0.20	0.94
	Previous 1–4 years	-0.09	0.31	0.77
	Previous 5–7 years	0.07	0.41	0.86
	Previous 8–10 years	0.85	0.79	0.28
Insulin secretagogues ^a and incretin mimetics ^b	Previous year	0.07	0.20	0.71
	Previous 1–4 years	0.24	0.33	0.48
	Previous 5–7 years	0.04	0.51	0.94
	Previous 8–10 years	-1.44	1.40	0.30
Alpha-glucosidase inhibitor	Previous year	1.47	1.03	0.15
	Previous 1–4 years	0.23	1.79	0.90
	Previous 5–7 years	-4.24	3.55	0.23
	Previous 8–10 years	5.99	3.30	0.07
Rosiglitazone	Previous year	0.93	0.86	0.28
	Previous 1–4 years	-1.32	1.35	0.33
	Previous 5–7 years	3.46	1.26	0.006
	Previous 8–10 years	-	-	-

DPP4i, dipeptidyl peptidase-4 inhibitors.

^a Sulfonylureas and meglitinides.

^b Dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists.