

Online-Only Supplemental Material

Title: Lp-PLA₂ activity is associated with increased risk of diabetic retinopathy: a longitudinal disease progression study

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Running head: Lp-PLA₂ activity and diabetic retinopathy

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Competing Risk: Association of Lp-PLA₂ and death in the GoDARTS cohort

ESM Table 1: Hazards ratios of death by Lp-PLA₂ quartiles in the GoDARTS cohort, adjusted for gender and age

Lp-PLA₂ quartiles	Hazard Ratios (95% CI)	P value
1	--	--
2	0.98 (0.84, 1.14)	0.77
3	1.26 (1.09, 1.46) **	0.002
4	1.45 (1.24, 1.68) ***	<0.0001

ESM Table 2. Hazard Ratios of Lp-PLA₂ quartiles in all model shown separately for each variable added to develop the final model

Variables in model	Hazard Ratios (95% Confidence Limits) of Lp-PLA ₂ quartiles	P-values
Development of incident DR from disease-free state (DR0 to DR1 or higher) n = 1013		
<i>Lp-PLA₂ quartiles</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.33 (1.08, 1.64)	0.0079
Lp-PLA ₂ Quartile 3 v. 1	1.56 (1.28, 1.90)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	1.52 (1.24, 1.86)	<0.0001
<i>Lp-PLA₂ quartiles + sex</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.37 (1.11, 1.68)	0.0033
Lp-PLA ₂ Quartile 3 v. 1	1.60 (1.31, 1.97)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	1.60 (1.31, 1.96)	<0.0001
<i>Lp-PLA₂ quartiles + sex + diabetic medication</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.38 (1.12, 1.70)	0.0024
Lp-PLA ₂ Quartile 3 v. 1	1.58 (1.30, 1.93)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	1.61 (1.32, 1.97)	<0.0001
<i>Lp-PLA₂ quartiles + sex + diabetic medication + use of statins</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.41 (1.14, 1.74)	0.0014
Lp-PLA ₂ Quartile 3 v. 1	1.63 (1.33, 1.98)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	1.71 (1.40, 2.10)	<0.0001
<i>Lp-PLA₂ quartiles + sex + diabetic medication + use of statins + HbA_{1c}</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.35 (1.08, 1.67)	0.0072
Lp-PLA ₂ Quartile 3 v. 1	1.56 (1.27, 1.91)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	1.70 (1.38, 2.09)	<0.0001
<i>Lp-PLA₂ quartiles + sex + diabetic medication + use of statins + HbA_{1c} + SBP</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.35 (1.08, 1.67)	0.0075
Lp-PLA ₂ Quartile 3 v. 1	1.53 (1.24, 1.88)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	1.69 (1.37, 2.08)	<0.0001
<i>Lp-PLA₂ quartiles + sex + diabetic medication + use of statins + HbA_{1c} + SBP + LDLc</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.52 (1.21, 1.91)	0.0004
Lp-PLA ₂ Quartile 3 v. 1	1.71 (1.37, 2.15)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	2.08 (1.64, 2.64)	<0.0001
<i>Lp-PLA₂ quartiles + sex + diabetic medication + use of statins + HbA_{1c} + SBP + LDLc + age</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.52 (1.21, 1.91)	0.0003
Lp-PLA ₂ Quartile 3 v. 1	1.72 (1.37, 2.16)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	2.08 (1.64, 2.63)t	<0.0001
Progression to observable or more severe DR from lower grades (DR0 or DR1 to DR2 or higher) n = 1241		
<i>Lp-PLA₂ quartiles</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.86 (1.29, 2.77)	0.0023
Lp-PLA ₂ Quartile 3 v. 1	2.33 (1.59, 3.42)	<0.001
Lp-PLA ₂ Quartile 4 v. 1	2.21 (1.46, 3.33)	0.0002
<i>Lp-PLA₂ quartiles + HbA_{1c}</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.69 (1.12, 2.55)	0.012
Lp-PLA ₂ Quartile 3 v. 1	2.11 (1.41, 3.17)	0.0003
Lp-PLA ₂ Quartile 4 v. 1	1.96 (1.27, 3.01)	0.002
<i>Lp-PLA₂ quartiles + HbA_{1c} + SBP</i>		

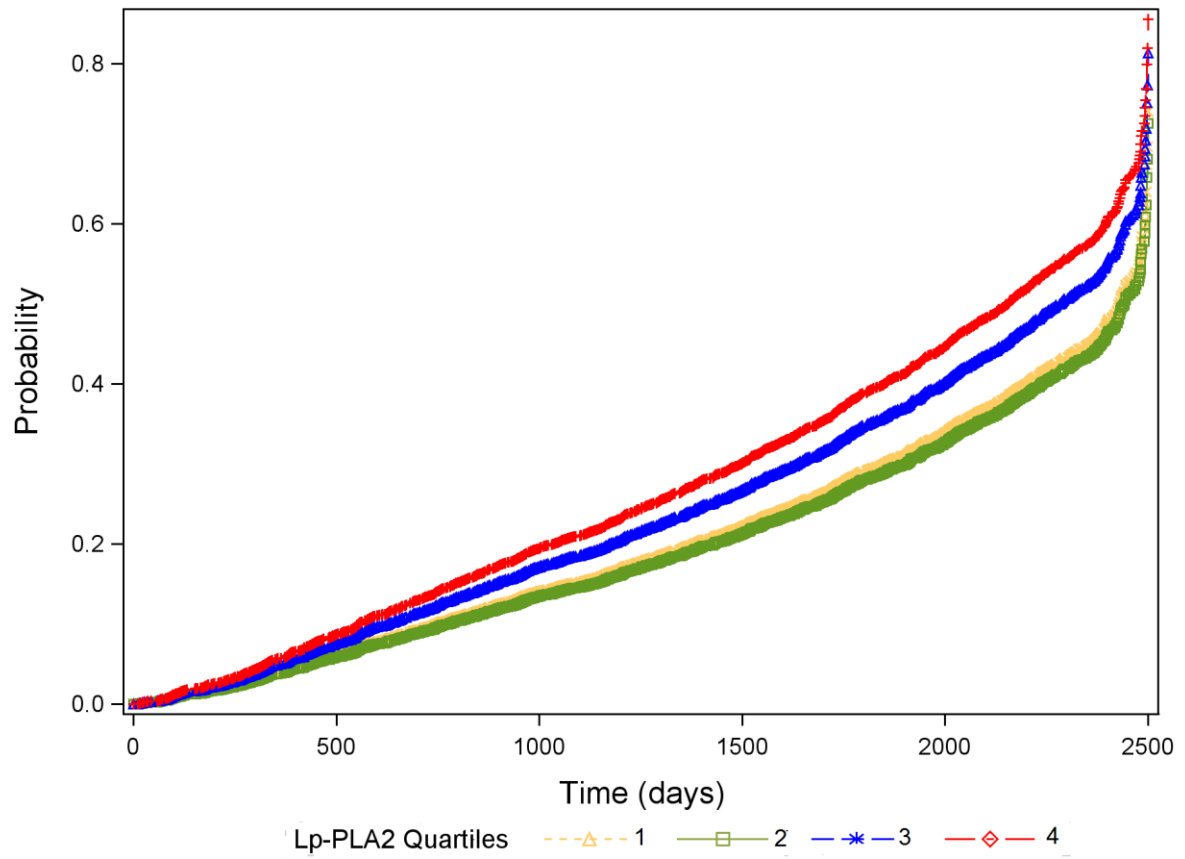
Lp-PLA ₂ Quartile 2 v. 1	1.70 (1.13, 2.56)	0.012
Lp-PLA ₂ Quartile 3 v. 1	2.11 (1.41, 3.17)	0.0003
Lp-PLA ₂ Quartile 4 v. 1	1.97 (1.28, 3.02)	0.002
<i>Lp-PLA₂ quartiles + HbA_{1c} + SBP + LDLc</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.91 (1.23, 2.99)	0.004
Lp-PLA ₂ Quartile 3 v. 1	2.52 (1.64, 3.88)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	2.43 (1.48, 3.97)	0.0004
<i>Lp-PLA₂ quartiles + HbA_{1c} + SBP + LDLc + age</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.91 (1.22, 2.99)	0.0045
Lp-PLA ₂ Quartile 3 v. 1	2.62 (1.70, 4.04)	<0.0001
Lp-PLA ₂ Quartile 4 v. 1	2.79 (1.70, 4.59)	<0.0001
Progression to referable or proliferative DR from lower grades (DR0, DR1 or DR2 to DR3 or higher) n = 1364		
<i>Lp-PLA₂ quartiles</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.76 (1.23, 2.50)	0.0018
Lp-PLA ₂ Quartile 3 v. 1	1.81 (1.26, 2.60)	0.0013
Lp-PLA ₂ Quartile 4 v. 1	1.83 (1.25, 2.66)	0.0017
<i>Lp-PLA₂ quartiles + DR grade at baseline</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.83 (1.28, 2.60)	0.0008
Lp-PLA ₂ Quartile 3 v. 1	1.89 (1.31, 2.73)	0.0006
Lp-PLA ₂ Quartile 4 v. 1	1.97 (1.35, 2.86)	0.0004
<i>Lp-PLA₂ quartiles + DR grade at baseline + use of diabetic medication</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.82 (1.28, 2.60)	0.0009
Lp-PLA ₂ Quartile 3 v. 1	1.96 (1.36, 2.83)	0.0003
Lp-PLA ₂ Quartile 4 v. 1	2.06 (1.42, 3.00)	0.0001
<i>Lp-PLA₂ quartiles + DR grade at baseline + use of diabetic medication + HbA_{1c}</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.70 (1.19, 2.45)	0.004
Lp-PLA ₂ Quartile 3 v. 1	1.88 (1.28, 2.76)	0.0014
Lp-PLA ₂ Quartile 4 v. 1	1.85 (1.26, 2.72)	0.0018
<i>Lp-PLA₂ quartiles + DR grade at baseline + use of diabetic medication + HbA_{1c} + SBP</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.70 (1.18, 2.44)	0.004
Lp-PLA ₂ Quartile 3 v. 1	1.87 (1.27, 2.74)	0.0015
Lp-PLA ₂ Quartile 4 v. 1	1.85 (1.25, 2.72)	0.002
<i>Lp-PLA₂ quartiles + DR grade at baseline + use of diabetic medication + HbA_{1c} + SBP + smoking status</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.74 (1.21, 2.50)	0.0027
Lp-PLA ₂ Quartile 3 v. 1	2.02 (1.36, 2.98)	0.0004
Lp-PLA ₂ Quartile 4 v. 1	1.97 (1.33, 2.93)	0.0008
<i>Lp-PLA₂ quartiles + DR grade at baseline + use of diabetic medication + HbA_{1c} + SBP + smoking status + age</i>		
Lp-PLA ₂ Quartile 2 v. 1	1.75 (1.22, 2.52)	0.0024
Lp-PLA ₂ Quartile 3 v. 1	2.06 (1.40, 3.04)	0.0003
Lp-PLA ₂ Quartile 4 v. 1	1.99 (1.34, 2.94)	0.0006

Sensitivity analysis – 5 year follow-up period

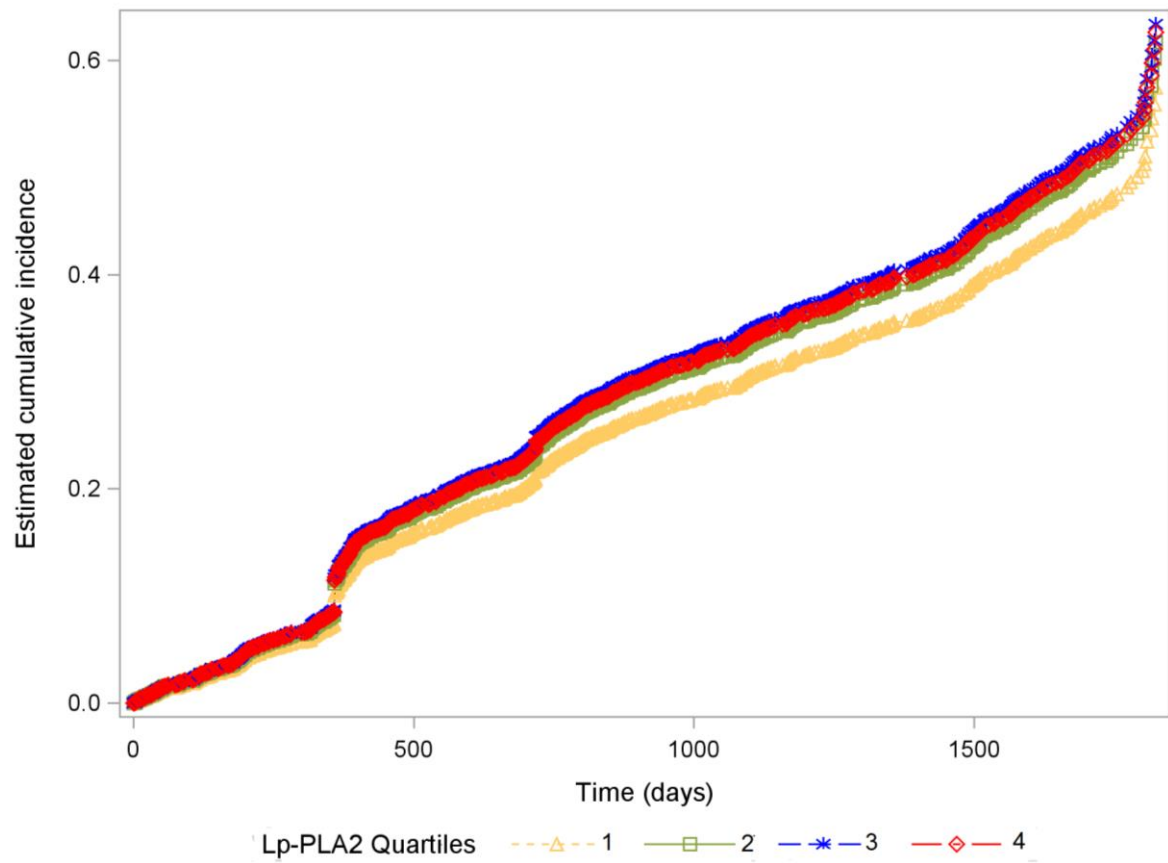
N = 2452, number of incident DR = 1038, number of competing events = 330, number censored = 1084

ESM Table 3 Hazard ratios for quartiles of Lp-PLA₂ at 5 years in a 5 year follow-up period

Lp-PLA ₂ quartiles	Hazard Ratios (95% CI)	P value
Main effects model		
Q1	--	--
Q2	1.12 (0.94, 1.35)	0.21
Q3	1.18 (0.99, 1.40)	0.06
Q4	1.15 (0.97, 1.37)	0.11
Adjusted model (adjusted for use of diabetic medication, lipid modifying medication, HbA1c, SBP, LDL, sex, and age)		
Q1	--	--
Q2	1.17 (0.95, 1.43)	0.13
Q3	1.14 (0.93, 1.40)	0.20
Q4	1.26 (1.02, 1.56)	0.03



ESM Fig 1 Survival Analysis – probability of death by Lp-PLA₂ quartiles in the GoDARTS cohort (n = 6371). The model was adjusted for gender and age



ESM Fig 2 Cumulative incidence plot for the main effect of Lp-PLA₂ quartiles on the development of incident DR adjusted for the competing risk of death in a 5 year follow-up period.