SUPPLEMENTARY MATERIAL FOR

The combined effect of lifestyle factors and polygenic scores on age at onset in Parkinson's disease

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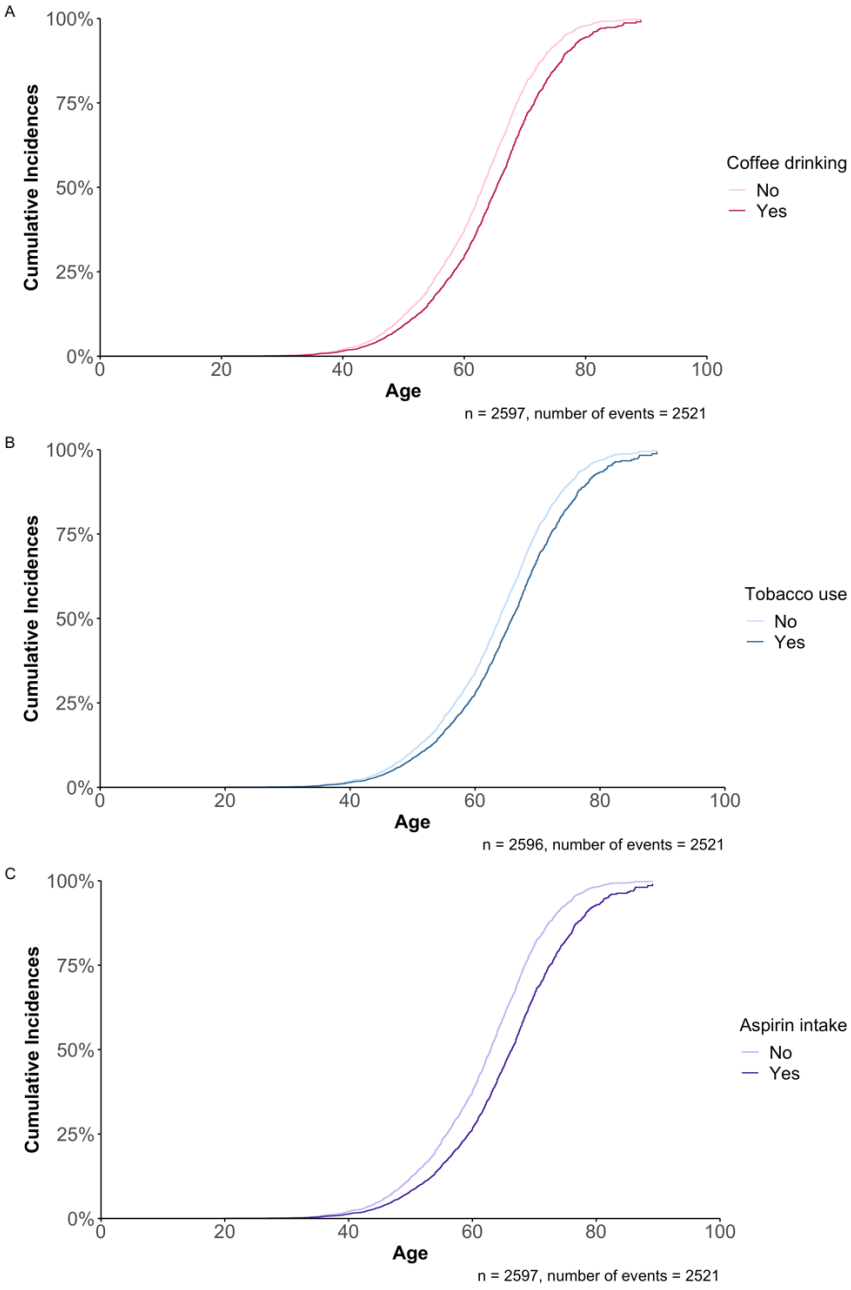
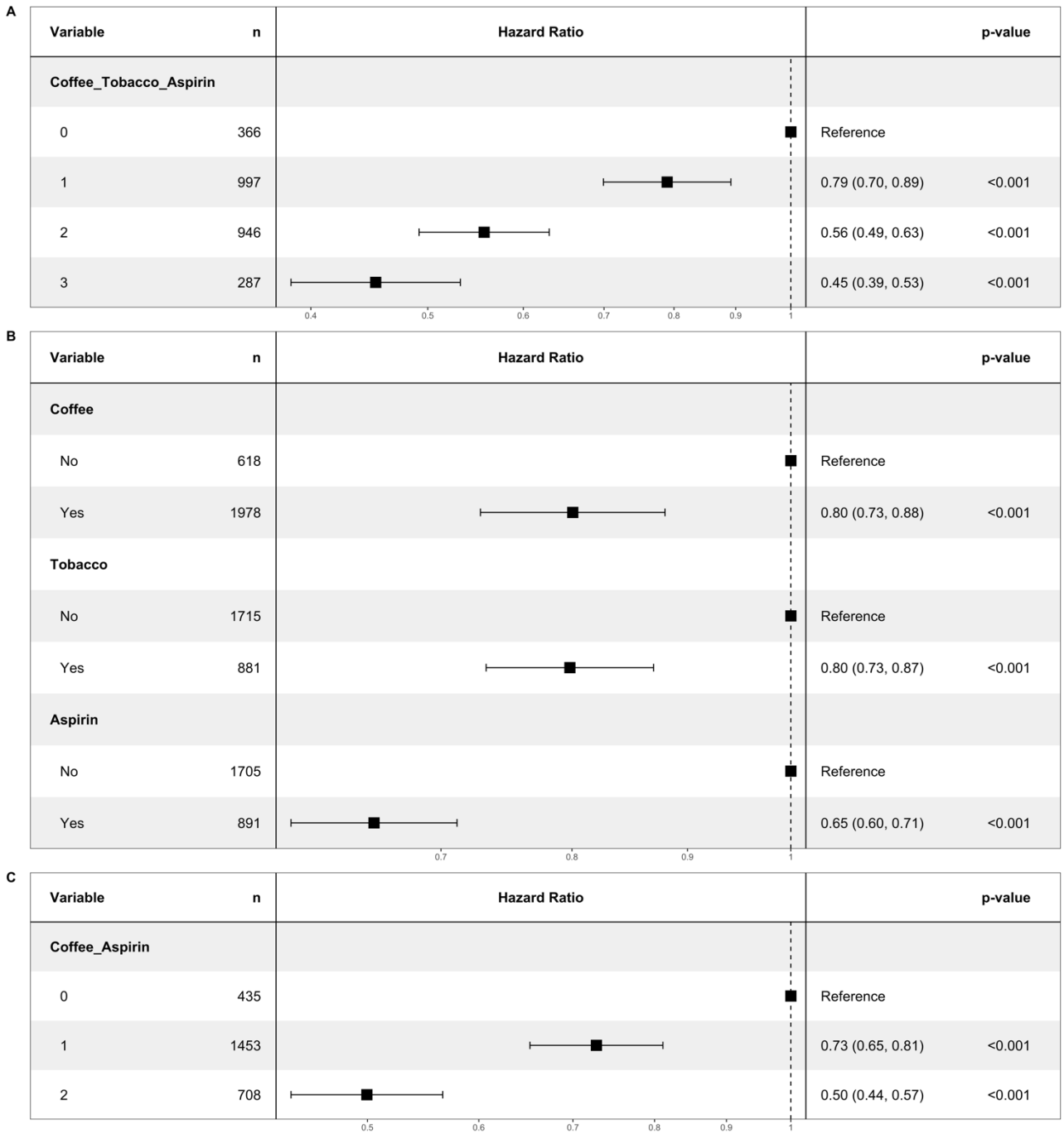
SUPPLEMENTARY FIGURES



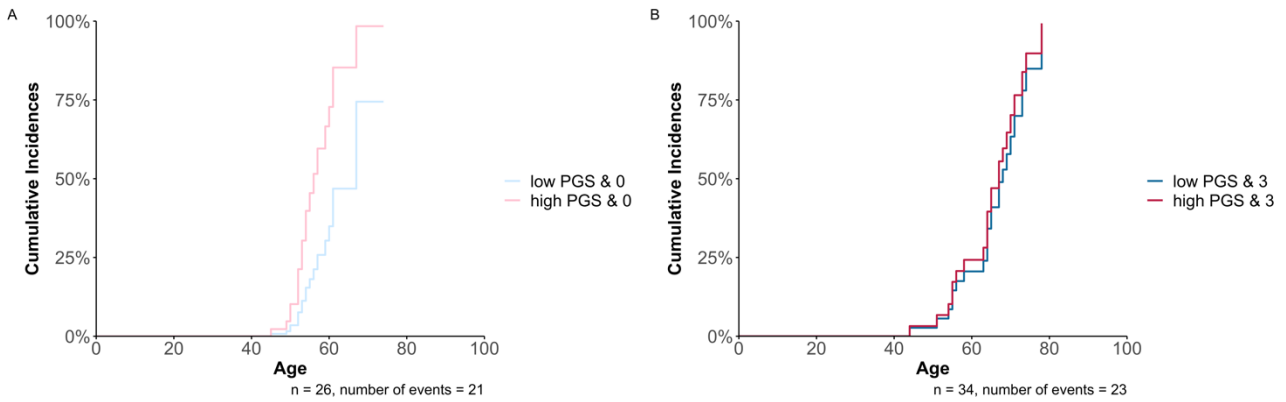
Supplementary Figure 1. Plot of the Cox proportional hazards models to investigate the association between the lifestyle factors coffee drinking, tobacco use, and aspirin intake on the AAO of PD patients, while censoring with the AAE of healthy controls.

(A) The different curves describe the coffee drinkers and non-coffee drinkers. A Cox proportional hazards model was used to investigate the difference in AAO while censoring with the AAE of healthy controls. The sex and the study site were additionally included as covariates (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ Coffee + Sex + Study, data = data)) **(B)** The different curves describe the tobacco users and non-tobacco users. A Cox proportional hazards model was used to investigate the difference in AAO while censoring with the AAE of healthy controls. The sex and the study site were additionally included as covariates (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ Tobacco + Sex + Study, data = data)) **(C)** The different curves describe the aspirin users and non-aspirin users. A Cox proportional hazards model was used to investigate the difference in AAO while censoring with the AAE of healthy controls. The sex and the study site were additionally included as covariates (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ Aspirin + Sex + Study, data = data))



Supplementary Figure 2. Plot of the Cox proportional hazards model to investigate the additive effects between the use of the lifestyle factors coffee drinking, tobacco use, and aspirin intake on the AAO of PD patients, while censoring with the AAE of healthy controls.

(A) The use of the lifestyle factors coffee drinking, tobacco use, and aspirin intake was used as cumulative number (0-3). The sex and study site were additionally included as covariables but are not displayed. (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ Coffee/Tobacco/Aspirin + Sex + Study, data = data)). **(B)** The lifestyle factors coffee drinking, tobacco use, and aspirin intake were included as separate covariables. The sex and study site were additionally included as covariables but are not displayed. (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ Coffee + Tobacco + Aspirin + Sex + Study, data = data)). **(C)** The use of the lifestyle factors coffee drinking and aspirin intake was used as cumulative number (0-2). The sex and study site were additionally included as covariables but are not displayed. (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ Coffee/Aspirin + Sex + Study, data = data)).



Supplementary Figure 3. Additive effects of the PGS and lifestyle factors on the AAO of PD patients, while censoring with the AAE of healthy controls.

(A) The different curves describe the PGS categorized into "low PGS" and "high PGS" according to the median PGS in the subgroup of participants that used no protective lifestyle factor. A Cox proportional hazards model was used to investigate the difference in AAO while censoring with the AAE of healthy controls. The sex and the first two PCs were additionally included (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ PGS low/high + Sex + PC1 + PC2, data = data_Coffee/Tobacco/Aspirin 0)). **(B)** The different curves describe the PGS categorized into "low PGS" and "high PGS" according to the median PGS in the subgroup of participants that used all three protective lifestyle factors. A Cox proportional hazards model was used to investigate the difference in AAO while censoring with the AAE of healthy controls. The sex and the first two PCs were additionally included (→ coxph(formula = Surv(AAO/AAE, Diagnosis) ~ PGS low/high + Sex + PC1 + PC2, data = data_Coffee/Tobacco/Aspirin 3)).

SUPPLEMENTARY TABLES

Supplementary Table 1. Linear model on the association of coffee drinking, tobacco use, and aspirin intake with AAO in the *GBA1*-PD study group

	Estimate	Standard error	*p*-value	
Coffee drinking (binary) (*n* = 145)[1]				
Intercept	58.8245	1.9240	**$<2x10^{-16}$**	*
Coffee drinking (binary)	3.3597	2.0773	0.1080	
Sex (Male)	0.5488	1.6176	0.7349	
Coffee drinking dosage (*n* = 113)[1]				
Intercept	60.7349	1.5662	**$<2x10^{-16}$**	*
Coffee drinking dosage	0.0791	0.1137	0.4878	
Sex (Male)	0.7757	1.7817	0.6641	
Coffee drinking duration (*n* = 93)[1]				
Intercept	55.2783	1.7340	**$<2x10^{-16}$**	*
Coffee drinking duration	0.2423	0.0455	**$7x10^{-7}$**	*
Sex (Male)	-0.4705	1.9440	0.8093	
Tobacco use (binary) (*n* = 149)[1]				
Intercept	60.2231	1.2026	**$<2x10^{-16}$**	*
Tobacco use (binary)	3.6527	1.5808	**0.0223**	*
Sex (Male)	0.9111	1.5198	0.5498	
Tobacco use dosage (*n* = 124)[1]				
Intercept	60.8739	1.2053	**$<2x10^{-16}$**	*
Tobacco use dosage	0.1386	0.0791	0.0823	
Sex (Male)	-0.2229	1.6733	0.8942	
Tobacco use duration (*n* = 121)[1]				
Intercept	60.7810	1.2286	**$<2x10^{-16}$**	*
Tobacco use duration	0.2193	0.0882	**0.0143**	*
Sex (Male)	0.3614	1.6704	0.8291	
Aspirin intake (binary) (*n* = 92)[1]				
Intercept	59.3073	1.6076	**$<2x10^{-16}$**	*
Aspirin intake (binary)	3.5143	2.2708	0.1253	
Sex (Male)	1.1559	2.0902	0.5816	
Aspirin intake dosage (*n* = 88)[1]				
Intercept	59.3123	1.4826	**$<2x10^{-16}$**	*
Aspirin intake dosage	0.4355	0.2213	0.0524	
Sex (Male)	1.5660	2.0077	0.4376	
Aspirin intake duration (*n* = 83)[1]				
Intercept	58.985	1.5121	**$<2x10^{-16}$**	*
Aspirin intake duration	0.4810	0.2066	**0.0224**	*
Sex (Male)	1.7848	2.0705	0.3913	
All lifestyle factors (binary) (*n* = 89)[2]				
Intercept	56.4789	2.7708	**$<2x10^{-16}$**	*
Coffee drinking (binary)	0.2295	2.8641	0.9363	
Tobacco use (binary)	6.7844	2.1707	**0.0024**	*
Aspirin intake (binary)	2.1989	2.2613	0.3336	
Sex (Male)	1.8093	2.0733	0.3853	

[1]glm(formula = AAO ~ Lifestyle factor + Sex, family = gaussian, data=data).
[2]glm(formula = AAO ~ Coffee drinking (binary) + Tobacco use (binary) + Aspirin intake (binary) + Sex, family = gaussian, data=data).
* *p*-value < 0.05 are highlighted in bold.
Abbreviations: AAO, age at onset; PD, Parkinson's disease; glm, generalized linear model.

Supplementary Table 2. Linear model on the association of coffee drinking, tobacco use, and aspirin intake with AAO using *GBA1* mutation carrier status (*GBA1*-PD vs. iPD) as another covariate

	Estimate	Standard error	*p*-value	
Coffee drinking (binary) (*n* = 2666)[1]				
Intercept	57.4021	0.4039	**$<2x10^{-16}$**	*
Coffee drinking (binary)	2.9247	0.4293	**$2x10^{-11}$**	*
Sex (Male)	1.1880	0.3657	**0.0012**	*
GBA1 mutation status (*GBA1*-PD)	1.4501	0.8007	0.0702	
Coffee drinking dosage (*n* = 2438)[1]				
Intercept	58.7078	0.3216	**$<2x10^{-16}$**	*
Coffee drinking dosage	0.0815	0.0193	**$2x10^{-5}$**	*
Sex (Male)	1.0858	0.3880	**0.0052**	*
GBA1 mutation status (*GBA1*-PD)	2.0984	0.8989	**0.0197**	*
Coffee drinking duration (*n* = 1816)[1]				
Intercept	55.5061	0.3723	**$<2x10^{-16}$**	*
Coffee drinking duration	0.1791	0.0099	**$<2x10^{-16}$**	*
Sex (Male)	-0.4503	0.4184	0.2821	
GBA1 mutation status (*GBA1*-PD)	1.4076	0.9306	0.1306	
Tobacco use (binary) (*n* = 2670)[1]				
Intercept	58.8585	0.2913	**$<2x10^{-16}$**	*
Tobacco use (binary)	2.0021	0.3847	**$2x10^{-7}$**	*
Sex (Male)	1.3576	0.3645	**0.0002**	*
GBA1 mutation status (*GBA1*-PD)	1.7411	0.7919	**0.0280**	*
Tobacco use dosage (*n* = 2410)[1]				
Intercept	59.1459	0.2808	**$<2x10^{-16}$**	*
Tobacco use dosage	0.0681	0.0125	**$6x10^{-8}$**	*
Sex (Male)	1.0795	0.3832	**0.0049**	*
GBA1 mutation status (*GBA1*-PD)	1.4818	0.8588	0.0846	
Tobacco use duration (*n* = 2180)[1]				
Intercept	59.9896	0.2977	**$<2x10^{-16}$**	*
Tobacco use duration	0.1311	0.0221	**$3x10^{-9}$**	*
Sex (Male)	0.9518	0.4015	**0.0178**	*
GBA1 mutation status (*GBA1*-PD)	1.8386	0.8750	**0.0357**	*
Aspirin intake (binary) (*n* = 2612)[1]				
Intercept	58.2492	0.2813	**$<2x10^{-16}$**	*
Aspirin intake (binary)	4.6349	0.3854	**$<2x10^{-16}$**	*
Sex (Male)	0.7787	0.3656	**0.0333**	*
GBA1 mutation status (*GBA1*-PD)	0.9098	0.9778	0.3522	
Aspirin intake dosage (*n* = 2495)[1]				
Intercept	58.8474	0.2811	**$<2x10^{-16}$**	*
Aspirin intake dosage	0.2684	0.0383	**$3x10^{-12}$**	*
Sex (Male)	1.0059	0.3757	**0.0075**	*
GBA1 mutation status (*GBA1*-PD)	1.1040	1.0053	0.2722	
Aspirin intake duration (*n* = 2166)[1]				
Intercept	58.6431	0.2888	**$<2x10^{-16}$**	*
Aspirin intake duration	0.2948	0.0285	**$<2x10^{-16}$**	*
Sex (Male)	0.5388	0.3982	0.1762	
GBA1 mutation status (*GBA1*-PD)	1.3935	1.0246	0.1739	
All lifestyle factors (binary) (*n* = 2610)[2]				
Intercept	56.1502	0.4099	**$<2x10^{-16}$**	*
Coffee drinking (binary)	2.3116	0.4313	**$9x10^{-8}$**	*
Tobacco use (binary)	1.5787	0.3858	**$4x10^{-5}$**	*
Aspirin intake (binary)	4.5174	0.3820	**$<2x10^{-16}$**	*
Sex (Male)	0.4930	0.3643	0.1761	
GBA1 mutation status (*GBA1*-PD)	0.5397	0.9842	0.5835	

[1]glm(formula = AAO ~ Lifestyle factor + Sex + *GBA1* mutation status, family = gaussian, data=data).
[2]glm(formula = AAO ~ Coffee drinking (binary) + Tobacco use (binary) + Aspirin intake (binary) + Sex + *GBA1* mutation status, family = gaussian, data=data).
* *p*-value < 0.05 are highlighted in bold.
Abbreviations: AAO, age at onset; PD, Parkinson's disease; glm, generalized linear model.