

# Supplementary Material

## Colonoscopy and Subsequent Risk of Parkinson's Disease

The supplementary material includes Supplementary Material 1, 2, and 3. In the first part, the reader can find the underlying EBM codes (outpatient sector; Einheitlicher Bewertungsmaßstab – uniform assessment standard) and OPS codes (inpatient sector; Operationen- und Prozedurenschlüssel – operation and procedure codes) that were used to categorize colonoscopy into the following groups: never received colonoscopy, colorectal cancer (CRC) screening without and with biopsy, destruction, excision, laser vaporization or argon plasma coagulation (BDE) and diagnostic colonoscopy without and with BDE. EBM and OPS codes changed over time. These changes have been accounted for. The second part includes scaled Schoenfeld residual plots for the estimated models to graphically verify the proportional hazard assumption. The third part contains a sensitivity analysis where the fully-adjusted competing risk model is stratified by sex and age group at baseline (first quarter of 2006; age <75 and age ≥75).

### Supplementary Material 1

**Supplementary Table 1.** EBM numbers for all types of colonoscopy

Period of use	EBM	Description
1 <sup>st</sup> quarter 2004 – 1 <sup>st</sup> quarter 2005	156	Total colonoscopy, including cecum (screening)
	163	Surcharge for number 156 for complete ablation of one or more polyps using a high-frequency electric snare
	755	Rectoscopy and/or sigmoidoscopy, including possible sample excision
	760	Partial colonoscopy with flexible instrument, including possible sample excision
	764	Total colonoscopy, including cecum, including possible sample excision
	765	Surcharge for number 740, 741, 755 to 764 for complete ablation of one or more polyps using a high-frequency electric snare
	775	Laser vaporization(s) in addition to endoscopic services
2 <sup>nd</sup> quarter 2005 – 4 <sup>th</sup> quarter 2019	01741	Screening
	01742	Surcharge for number 01741 for ablation of polyps
	13421	Additional fee colonoscopy
	13422	Additional fee partial colonoscopy
	13423	Additional service(s) for number 13421 or 13422 (foreign body removal, polypectomy(s), snare biopsy, hemostasis]
13424	Additional service(s) for number 13400, 13421 or 13422 (laser vaporization(s) and/or argon plasma coagulation(s))	

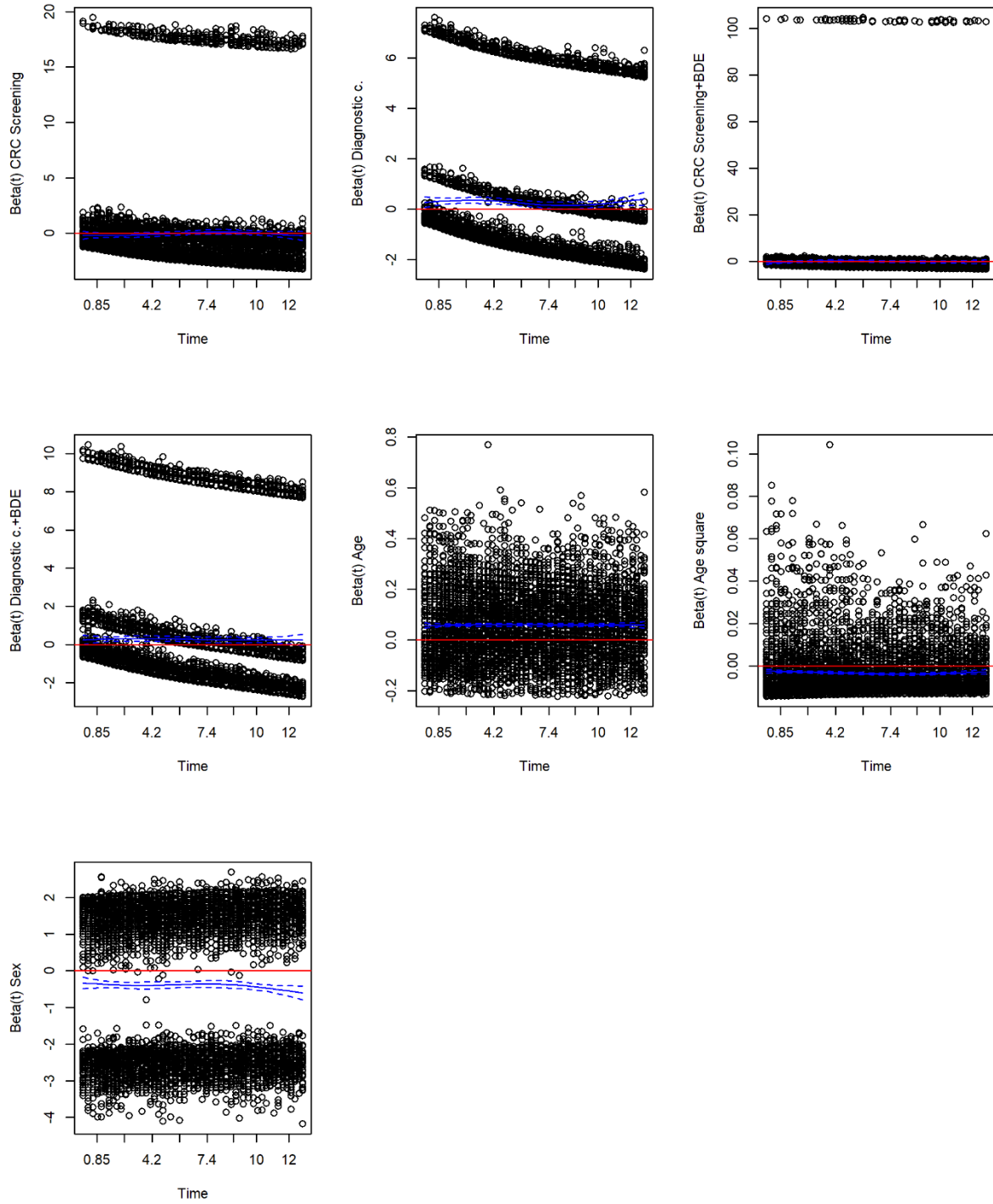
**Supplementary Table 2.** OPS numbers for all types of colonoscopy

<b>Period of use</b>	<b>OPS</b>	<b>Description</b>
1 <sup>st</sup> quarter 2004 – 1 <sup>st</sup> quarter 2019	<b>1650</b>	<b>Diagnostic colonoscopy</b>
	16500	Partial
	16501	Total, including cecum
	16502	Total, with ileoscopy
	1650x	Other
	1650y	Not further specified
	1651	Diagnostic sigmoideoscopy
	1652	Diagnostic endoscopy of the intestine via a stoma
	16521	Colonoscopy
	16522	Sigmoideoscopy
	<b>1444</b>	<b>Endoscopic biopsy of the lower digestive tract</b>
	14446	Step biopsy
	14447	1 to 5 biopsies
	1444x	Other
	1444y	Not further specified
1 <sup>st</sup> quarter 2004 – 4 <sup>th</sup> quarter 2011	<b>5452</b>	<b>Local excision and destruction of diseased tissue of the colon</b>
	<b>54522</b>	<b>Excision, endoscopic</b>
	545220	Excision without further measures
	545221	Polypectomy of 1-2 polyps with snare
	545222	Polypectomy of 2 or more polyps with snare
	545223	Endoscopic mucosal resection
	54522x	Other
	<b>54525</b>	<b>Destruction, endoscopic</b>
	545250	Electrocoagulation
	545251	Lasercoagulation
	545252	Thermocoagulation
	545253	Cryocoagulation
	545254	Photodynamic therapy
	54525x	Other
	1 <sup>st</sup> quarter 2012 – 4 <sup>th</sup> quarter 2015	5452
54522		<b>Excision, endoscopic</b>
545220		Excision without further measures
545221		Polypectomy of 1-2 polyps with snare
545222		Polypectomy of 2 or more polyps with snare
545223		Endoscopic mucosal resection
545224		Endoscopic submucosal dissection (ESD)
54522x		Other
54525		<b>Destruction, endoscopic</b>
545250		Electrocoagulation
545251		Lasercoagulation
545252		Thermocoagulation
545253		Cryocoagulation
545254		Photodynamic therapy
54525x		Other
1 <sup>st</sup> quarter 2016 – 4 <sup>th</sup> quarter 2016	5452	<b>Local excision and destruction of diseased tissue of the colon</b>
	54522	<b>Excision, endoscopic</b>
	545220	Excision without further measures

	545221	Polypectomy of 1-2 polyps with snare
	545222	Polypectomy of 2 or more polyps with snare
	545223	Endoscopic mucosal resection
	545224	Endoscopic submucosal dissection
	545225	Endoscopic solid wall excision
	54522x	Other
	54525	<b>Destruction, endoscopic</b>
	545250	Electrocoagulation
	545251	Lasercoagulation
	545252	Thermocoagulation
	545253	Cryocoagulation
	545254	Photodynamic therapy
	54525x	Other
1 <sup>st</sup> quarter 2017 – 4 <sup>th</sup> quarter 2019	54526	<b>Excision, endoscopic, simple (push technique)</b>
	545260	Excision without further measures
	545261	Polypectomy of 1-2 polyps with snare
	545262	Polypectomy of 2 or more polyps with snare
	545263	Endoscopic mucosal resection
	545264	Endoscopic submucosal dissection
	545265	Endoscopic solid wall excision
	54526x	Other
	54527	<b>Excision, endoscopic, push-and-pull-back technique</b>
	545270	Excision without further measures
	545271	Polypectomy of 1-2 polyps with snare
	545272	Polypectomy of 2 or more polyps with snare
	545273	Endoscopic mucosal resection
	545274	Endoscopic submucosal dissection
	54527x	Other
	54528**	<b>Destruction, endoscopic, simple (push technique)</b>
	545280	Electrocoagulation
	545281	Lasercoagulation
	545282	Thermocoagulation
	545283	Cryocoagulation
	545284	Photodynamic therapy
	54528x	Other
	54529**	<b>Destruction, endoscopic, push-and-pull-back technique</b>
	545290	Electrocoagulation
	545291	Lasercoagulation
	545292	Thermocoagulation
	545293	Cryocoagulation
	545294	Photodynamic therapy
	54529x	Other

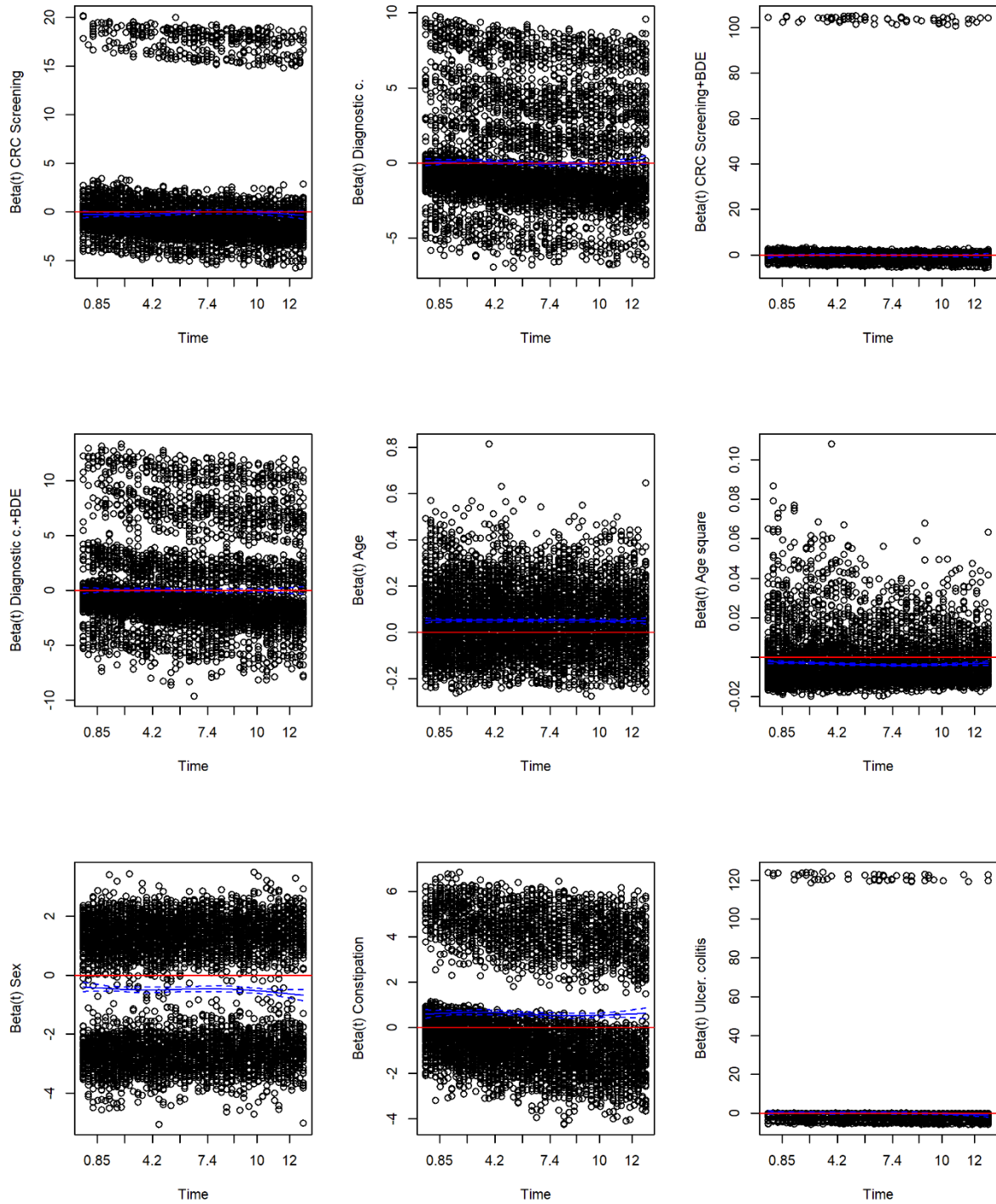
## Supplementary Material 2

### Supplementary Figure 1. Scaled Schoenfeld Residuals for Model 1 (Cox model)

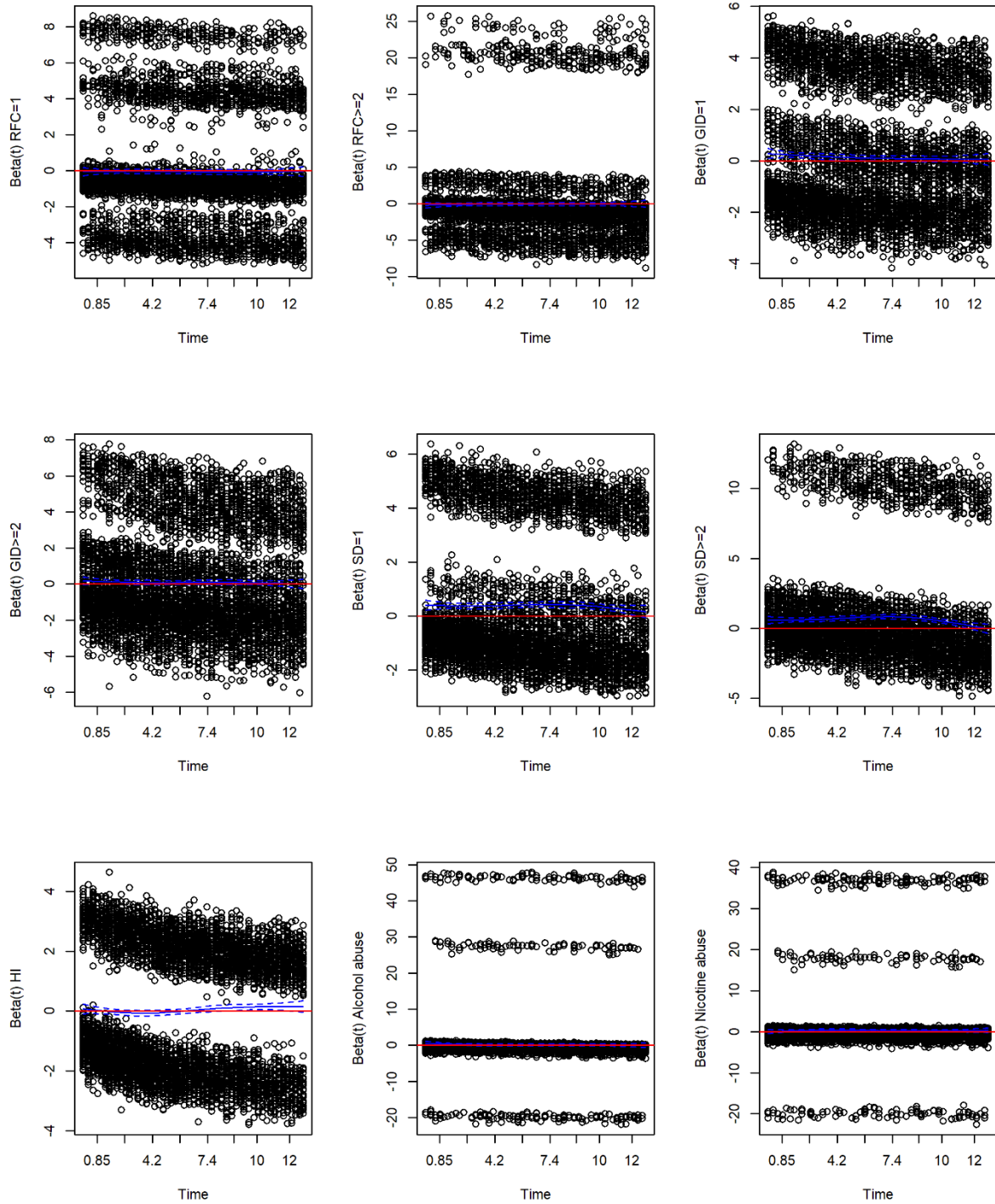


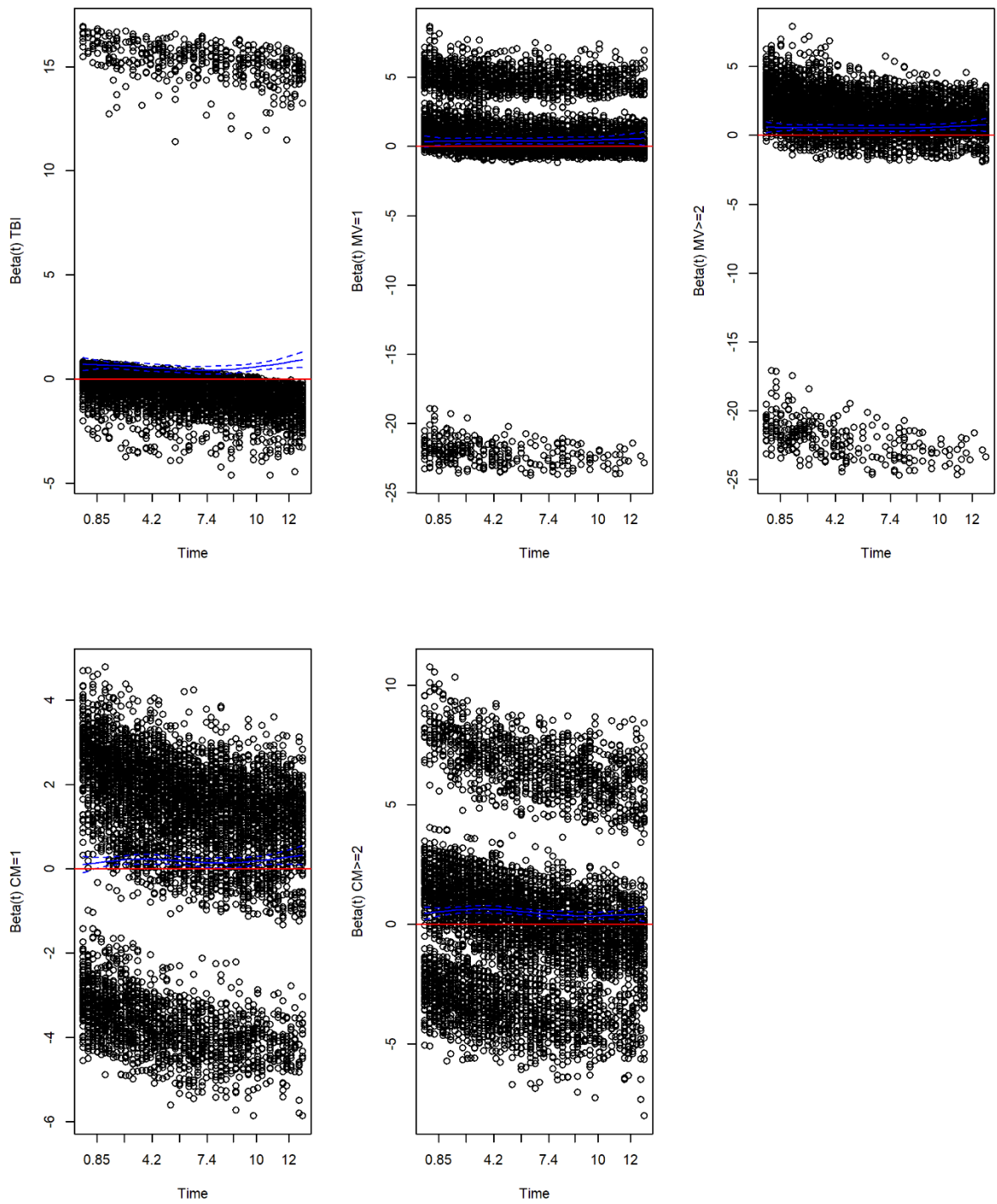
Scaled Schoenfeld Residuals for Model 1. Red line: zero position, blue line: Beta(t) with 95% confidence interval. Source: Source: AOK 2004-2019

Supplementary Figure 2. Scaled Schoenfeld Residuals for Model 2 (Cox model)



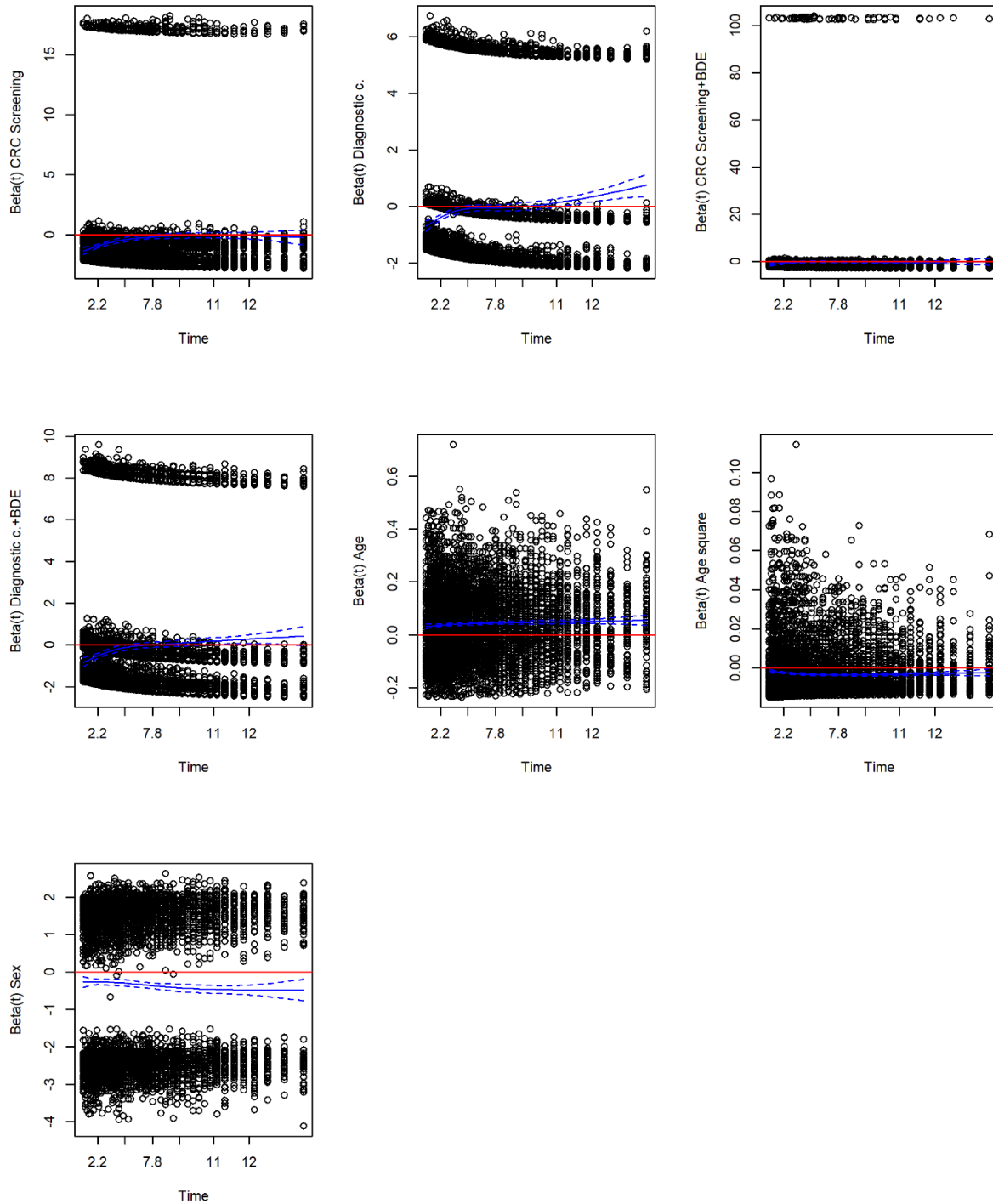
## Supplementary Figure 2 (continued)





Scaled Schoenfeld Residuals for Model 2. Red line: zero position, blue line: Beta(t) with 95% confidence interval. Source: Source: AOK 2004-2019

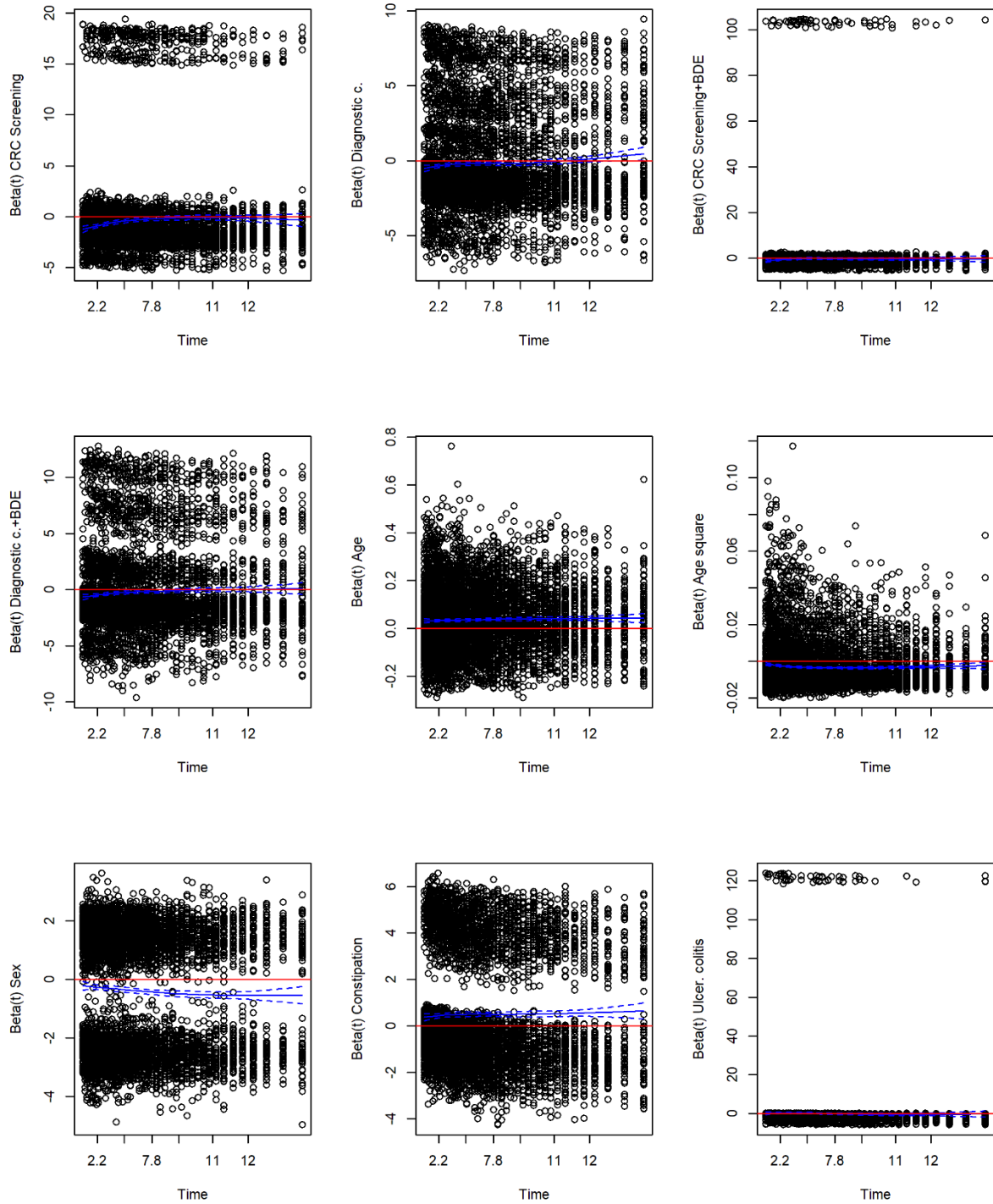
Supplementary Figure 3. Scaled Schoenfeld Residuals for Model 3 (Competing-risk model)



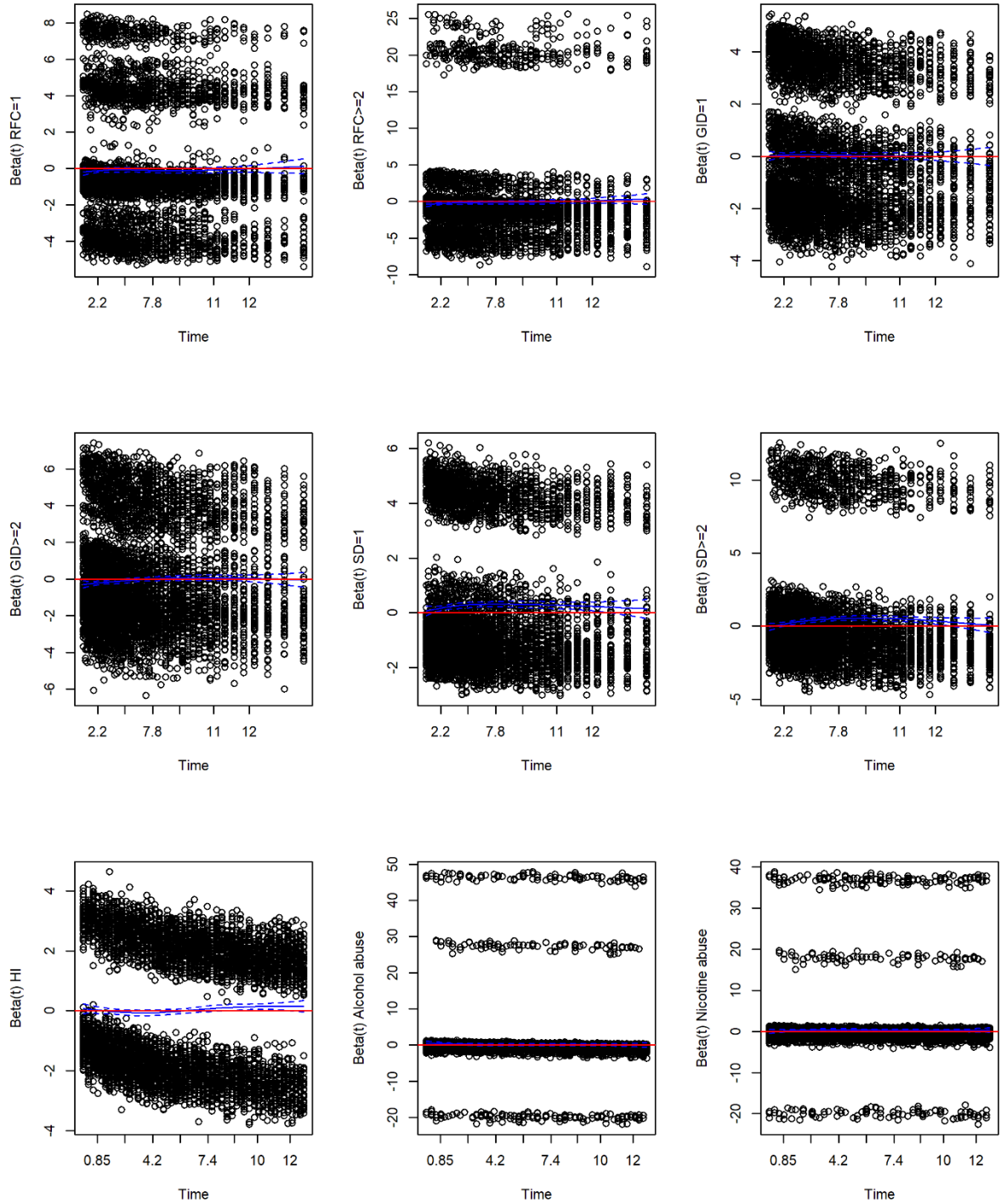
Scaled Schoenfeld Residuals for Model 3. Red line: zero position, blue line: Beta(t) with 95% confidence interval. Source: Source: AOK 2004-2019

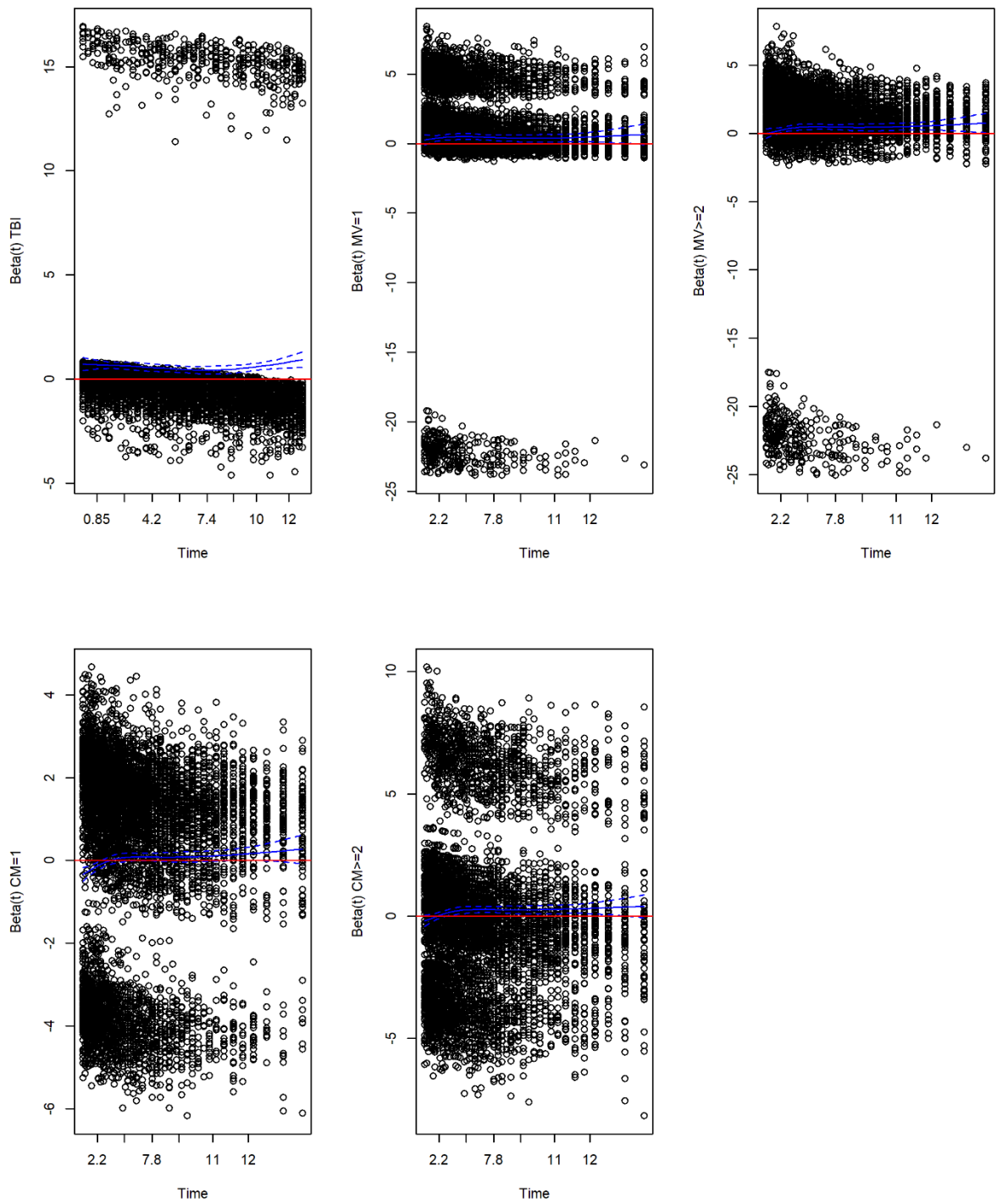


Supplementary Figure 4. Scaled Schoenfeld Residuals for Model 4 (Competing-risk model)



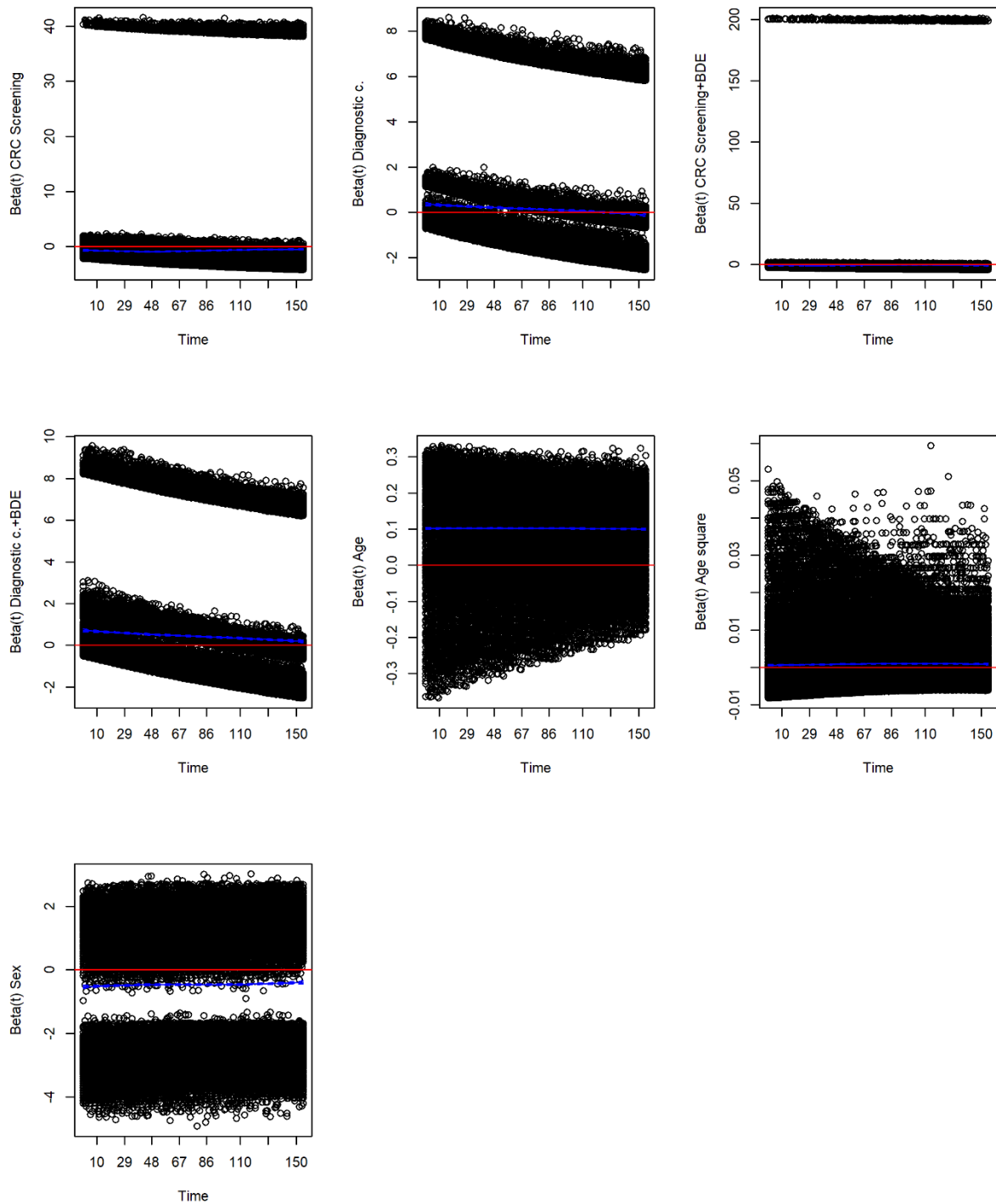
Supplementary Figure 4 (continued)





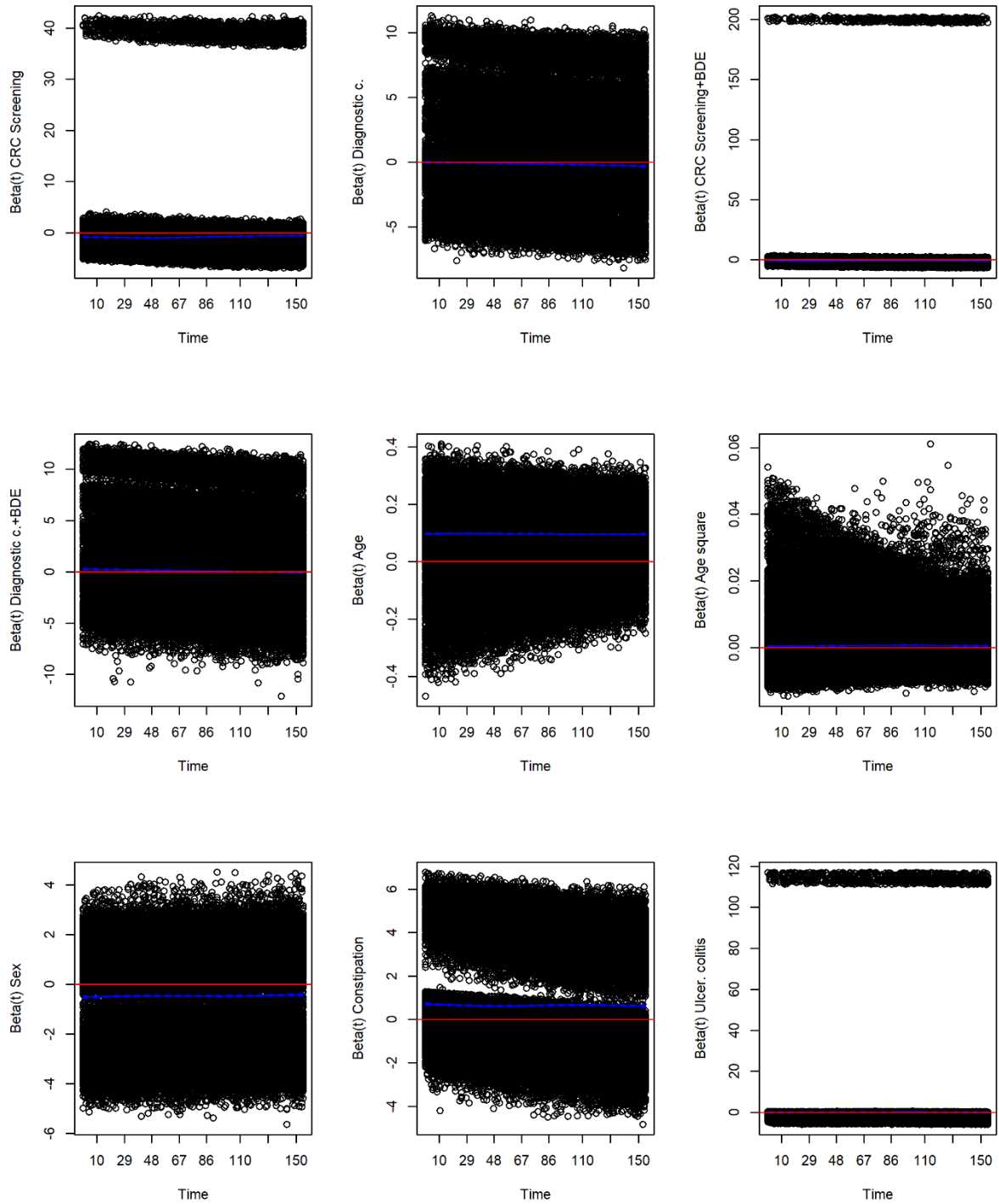
Scaled Schoenfeld Residuals for Model 4. Red line: zero position, blue line:  $\beta(t)$  with 95% confidence interval. Source: Source: AOK 2004-2019

Supplementary Figure 5. Scaled Schoenfeld Residuals for Model 5 (Outcome: Death)

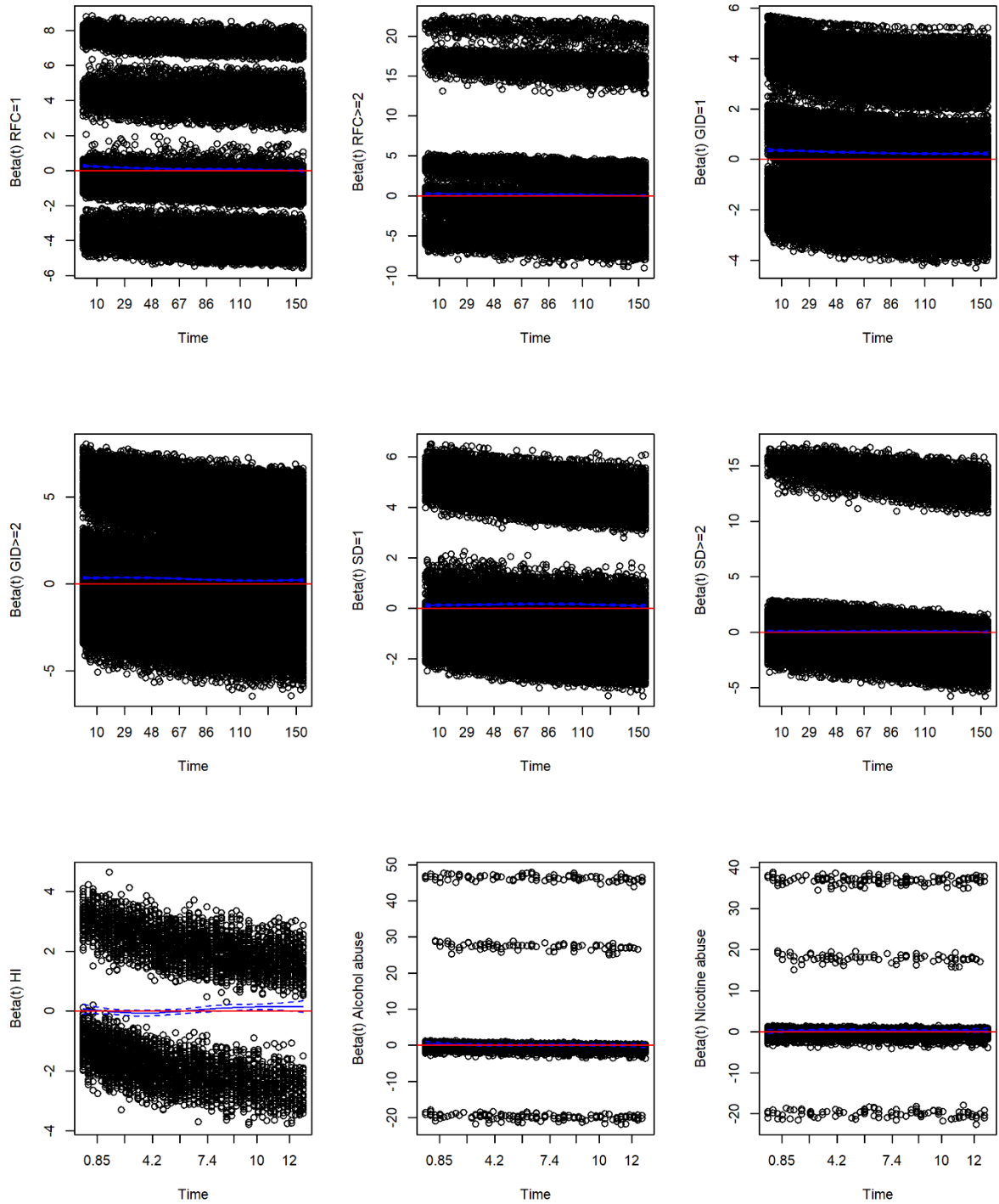


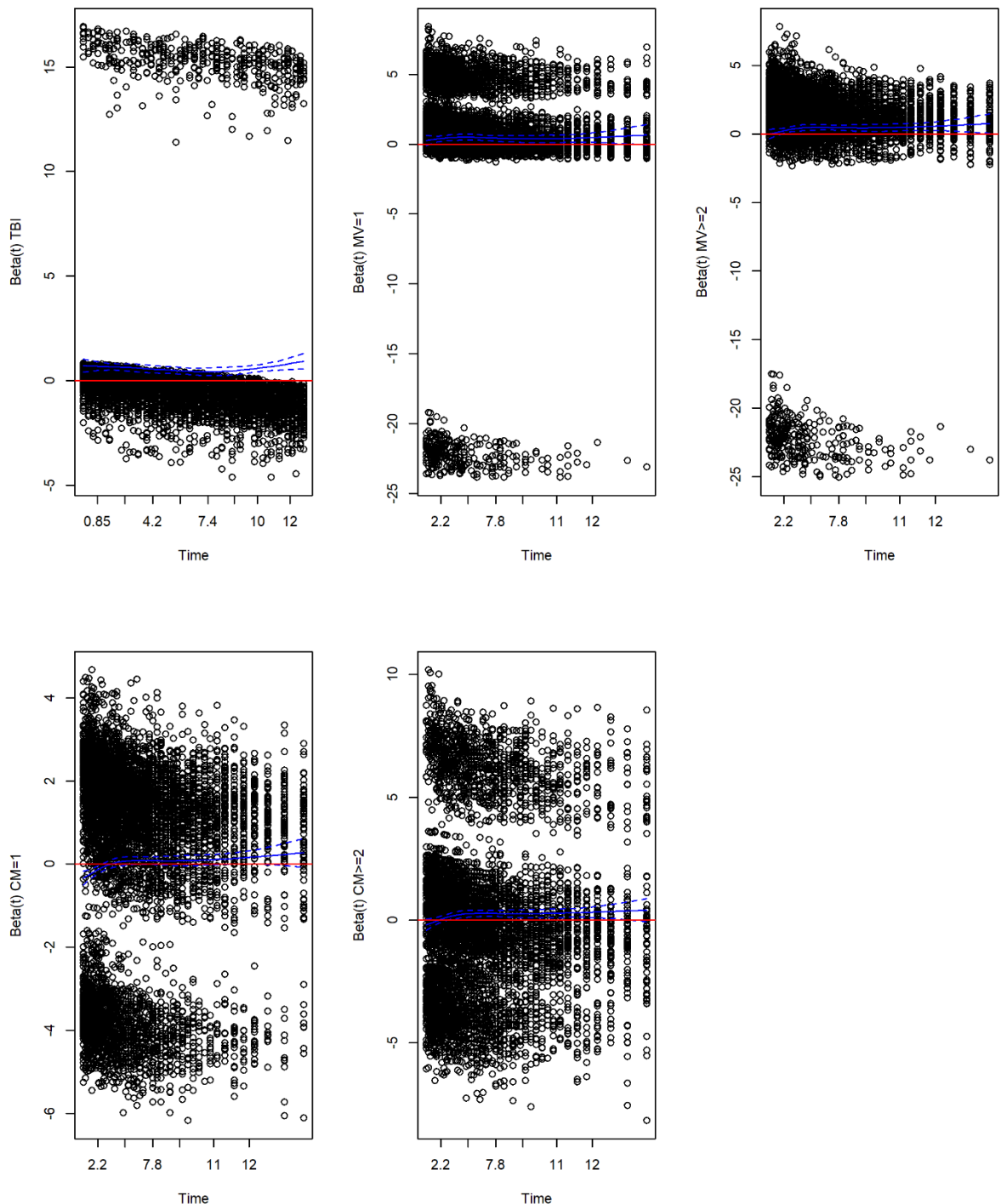
Scaled Schoenfeld Residuals for Model 5. Red line: zero position, blue line: Beta(t) with 95% confidence interval. Source: Source: AOK 2004-2019

Supplementary Figure 6. Scaled Schoenfeld Residuals for Model 6 (Outcome: Death)



Supplementary Figure 6 (continued)





Scaled Schoenfeld Residuals for Model 6. Red line: zero position, blue line: Beta(t) with 95% confidence interval. Source: Source: AOK 2004-2019  
 RFC, reasons for colonoscopy; GID, gastrointestinal disorders; SD, sleep disorders, HI, hearing impairment; TBI, traumatic brain injury; MV, metabolic and cardiovascular disorders; CM, other co-morbidities

### Supplementary Material 3

**Supplementary Table 3.** Fully adjusted competing risk model for the risk of Parkinson's disease (PD) by sex and age group at baseline

Risk of PD		<i>Women, age &lt;75</i>		<i>Women, age ≥75</i>		<i>Men, age &lt;75</i>		<i>Men, age ≥75</i>	
		CRHR** [95% CI]	p	CRHR** [95% CI]	p	CRHR** [95% CI]	p	CRHR** [95% CI]	p
<b>Colonoscopy (Ref. never)</b>									
CRC screening without BDE		0.68 [0.57-0.82]	<0.001	0.81 [0.57-1.15]	0.247	0.93 [0.78-1.09]	0.361	0.87 [0.59-1.29]	0.494
Diagnostic colonoscopy without BDE		0.94 [0.83-1.08]	0.381	1.02 [0.86-1.20]	0.834	1.03 [0.90-1.17]	0.671	1.07 [0.87-1.33]	0.509
CRC screening with BDE		0.79 [0.49-1.28]	0.333	0.75 [0.28-2.00]	0.567	0.81 [0.57-1.15]	0.234	1.08 [0.56-2.10]	0.815
Diagnostic colonoscopy with BDE		0.99 [0.83-1.17]	0.883	1.01 [0.83-1.22]	0.953	1.08 [0.94-1.25]	0.283	1.06 [0.84-1.33]	0.637
<b>Reason for colonoscopy and prodromal symptom/risk for PD</b>									
Constipation (Ref. no)		2.18 [1.96-2.43]	<0.001	1.75 [1.56-1.96]	<0.001	2.25 [2.02-2.51]	<0.001	1.67 [1.43-1.96]	<0.001
Ulcerative colitis (Ref. no)		1.29 [0.82-2.03]	0.275	1.32 [0.76-2.30]	0.320	0.74 [0.43-1.25]	0.255	1.18 [0.56-2.50]	0.658
<b>Reasons for colonoscopy (Ref. no)</b>	1	1.01 [0.88-1.14]	0.931	0.95 [0.81-1.10]	0.471	1.04 [0.92-1.17]	0.549	1.01 [0.83-1.22]	0.924
	2 or more	1.12 [0.90-1.38]	0.312	0.82 [0.62-1.08]	0.164	1.00 [0.80-1.24]	0.992	0.97 [0.69-1.36]	0.863
<b>Gastrointestinal disorders (Ref. no)</b>	1	1.15 [1.02-1.28]	0.017	1.24 [1.10-1.39]	0.001	1.07 [0.96-1.19]	0.227	1.12 [0.95-1.31]	0.163
	2 or more	1.06 [0.93-1.20]	0.373	1.19 [1.03-1.38]	0.017	1.05 [0.93-1.18]	0.407	0.95 [0.79-1.16]	0.633
<b>Sleep disorders (Ref. no)</b>	1	1.44 [1.29-1.60]	<0.001	1.42 [1.26-1.60]	<0.001	1.34 [1.20-1.49]	<0.001	1.53 [1.30-1.80]	<0.001
	2 or more	1.65 [1.42-1.91]	<0.001	2.14 [1.80-2.54]	<0.001	1.81 [1.56-2.10]	<0.001	1.37 [1.01-1.87]	0.044
<b>Hearing impairment (Ref. no)</b>		1.19 [1.09-1.31]	<0.001	1.03 [0.93-1.14]	0.558	1.16 [1.06-1.27]	0.001	0.97 [0.84-1.11]	0.640
<b>Behavioral risk factors for PD</b>									
Alcohol abuse (Ref. no)		1.07 [0.71-1.61]	0.752	1.48 [0.74-2.99]	0.270	0.98 [0.79-1.20]	0.824	1.31 [0.81-2.12]	0.267
Nicotine abuse (Ref. no)		1.18 [0.83-1.68]	0.350	0.94 [0.45-1.97]	0.868	1.07 [0.89-1.29]	0.469	1.53 [1.00-2.36]	0.051
TBI (Ref. no)		2.05 [1.69-2.49]	<0.001	1.71 [1.42-2.04]	<0.001	1.77 [1.48-2.12]	<0.001	2.10 [1.64-2.70]	<0.001
<b>Metabolic and cardiovascular disorders (Ref. no)</b>	1	1.74 [1.38-2.19]	<0.001	1.94 [1.39-2.70]	<0.001	1.78 [1.45-2.19]	<0.001	1.73 [1.23-2.44]	0.002
	2 or more	2.51 [2.02-3.12]	<0.001	2.20 [1.59-3.04]	<0.001	2.55 [2.11-3.09]	<0.001	1.85 [1.32-2.58]	<0.001
<b>Other comorbidities (Ref. no)</b>	1	1.37 [1.21-1.54]	<0.001	1.03 [0.91-1.17]	0.599	1.40 [1.26-1.55]	<0.001	1.16 [1.00-1.35]	0.050
	2 or more	1.57 [1.35-1.81]	<0.001	1.26 [1.07-1.50]	0.007	2.13 [1.84-2.46]	<0.001	1.60 [1.26-2.03]	<0.001

Competing risk regression models by age group and sex. Competing risk: Death; CRHR, competing risk hazard ratio; \*\*adjusted for colonoscopy, age, sex, reasons for colonoscopy and comorbidities of PD; CRC, colorectal cancer; BDE, biopsy, destruction, polyp removal, laser vaporization or argon plasma coagulation; TBI, traumatic brain injury. n=221,582. Source: AOK 2004-2019