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# Biomarkers as precursors of disability:

## Online Supplement

Table S1: Sample size for the single period prediction models.

Marker	Any or # difficulties			Mobility			Benefit receipt		
	<i>Prediction horizon</i>								
	<i>t</i> = 2	<i>t</i> = 3	<i>t</i> = 4	<i>t</i> = 2	<i>t</i> = 3	<i>t</i> = 4	<i>t</i> = 2	<i>t</i> = 3	<i>t</i> = 4
<i>Nurse measured biomarkers</i>									
Waist/height ratio	12025	11423	7671	13969	13242	8915	14492	13719	9256
Grip strength	11552	10972	7398	13351	12655	8561	13839	13101	8875
Hypertension	9993	9512	6409	11624	11032	7454	12142	11496	7771
Heart rate	10003	9522	6415	11639	11047	7463	12163	11516	7783
FVC	10832	10305	7013	12518	11887	8106	12947	12281	8395
<i>Blood-based biomarkers</i>									
HDL	7904	7488	5020	9176	8671	5831	9585	9047	6097
CRP	7591	7184	4813	8794	8306	5583	9152	8636	5809
HbA1c	7495	7104	4757	8716	8241	5540	9101	8598	5789
DHEA-S	7910	7496	5022	9180	8677	5835	9588	9052	6099
EGFR	7921	7502	5033	9197	8688	5848	9605	9063	6112
Hgb	7492	7098	4753	8712	8234	5537	9096	8590	5785
Albumin	7930	7511	5040	9207	8699	5856	9616	9075	6121
<i>Systematic risk scores</i>									
Allostatic load	5820	5529	3705	6740	6383	4298	7028	6652	4484
CVD risk	5842	5550	3723	6770	6412	4321	7056	6679	4506

Table S2: Survey question design: list of functional difficulties

Difficulty	Sample prevalence at..		
	<i>t</i> = 2	<i>t</i> = 3	<i>t</i> = 4
Mobility (moving around at home and walking)	0.040	0.045	0.053
Lifting, carrying or moving objects	0.046	0.048	0.051
Manual dexterity (using your hands to carry out everyday tasks)	0.014	0.015	0.016
Continence (bladder and bowel control)	0.010	0.012	0.011
Hearing (apart from using a standard hearing aid)	0.010	0.012	0.014
Sight (apart from wearing standard glasses)	0.008	0.009	0.009
Communication or speech problems	0.002	0.003	0.003
Memory or ability to concentrate, learn or understand	0.014	0.016	0.016
Recognising when you are in physical danger	0.002	0.002	0.002
Your physical co-ordination (e.g. balance)	0.013	0.015	0.016
Difficulties with own personal care (e.g. getting dressed, taking a bath or shower)	0.006	0.006	0.008
Other health problem or disability	0.025	0.029	0.035

Prevalence rates are for the individuals who report no functional difficulties at baseline. For *t* = 2,3, prevalence relates to the combined UKHLS/BHPS sample; for *t* = 4, prevalence relates to the UKHLS sample only.

Table S3: Mean biomarker levels and systemic risk scores by disability status 4 years ahead: measures based on number of functional difficulties reported

Biomarker	Any difficulty			Number of difficulties				Crude effect size (%)
	Non-disabled	Dis-abled	Crude effect size (%)	0	1	2	3+	
<i>Nurse measured biomarkers</i>								
Waist/height ratio	0.55	0.58	<b>-39.4</b>	0.55	0.57	0.58	0.59	<b>-54.7</b>
Grip strength (kg)	35.3	32.4	<b>25.9</b>	35.3	33.4	32.5	29.4	<b>52.0</b>
Hypertension	0.26	0.40	<b>-35.2</b>	0.26	0.40	0.42	0.47	<b>-46.8</b>
Heart rate (bpm)	68.5	69.7	<b>-12.0</b>	68.5	69.0	70.8	70.3	<b>-17.6</b>
FVC (L)	4.00	3.57	<b>41.2</b>	4.00	3.64	3.50	3.46	<b>51.9</b>
<i>Blood-based biomarkers</i>								
HDL (mmol/L)	1.59	1.52	<b>16.7</b>	1.59	1.50	1.56	1.52	<b>14.7</b>
CRP (mg/L)	1.80	2.33	<b>-28.3</b>	1.80	2.40	2.24	2.22	<b>-22.9</b>
HbA1c (mmol/mol)	36.1	38.7	<b>-38.8</b>	36.1	38.4	39.1	39.0	<b>-45.7</b>
DHEAS ( $\mu$ mol/L)	4.89	3.86	<b>33.4</b>	4.89	3.86	3.93	3.78	<b>35.4</b>
EGFR	92.8	85.7	<b>38.9</b>	92.8	86.3	85.1	84.5	<b>45.9</b>
Hgb (g/L)	137.4	136.3	8.2	137.4	136.9	135.9	135.3	15.9
Albumin (g/L)	47.2	46.3	<b>30.4</b>	47.2	46.6	46.1	45.9	<b>48.1</b>
<i>Systematic risk scores</i>								
Allostatic load	-0.21	1.75	<b>-47.9</b>	-0.21	1.60	1.62	2.50	<b>-66.5</b>
CVD risk score	-0.04	1.11	<b>-38.7</b>	-0.04	1.07	0.96	1.52	<b>-52.9</b>

Notes: Crude effect size is the difference in the mean biomarker/risk score values by disability status, expressed as percentage of the standard deviation of the biomarker/risk score; the lowest (zero) and highest (3+) groups are used in the case of the “number of difficulties” disability measure. Bold type indicates statistical significance at the 1% level (bootstrap with 500 replications). A negative effect size indicates that the biomarker/risk score has a higher mean value for the more disabled group.

Table S4: Mean biomarker levels and systemic risk scores by disability status 4 years ahead: mobility and benefit disability measures

Biomarker	Mobility			Benefit receipt		
	Non-abled	Dis-abled	Crude effect size (%)	Non-abled	Dis-abled	Crude effect size (%)
<i>Nurse measured biomarkers</i>						
Waist/height ratio	0.55	0.60	<b>-61.0</b>	0.56	0.60	<b>-51.9</b>
Grip strength (kg)	34.7	31.0	<b>32.9</b>	34.4	29.6	<b>42.3</b>
Hypertension	0.28	0.49	<b>-45.7</b>	0.30	0.45	-31.6
Heart rate (bpm)	68.6	70.2	<b>-15.2</b>	68.6	70.9	<b>-21.3</b>
FVC (L)	3.93	3.40	<b>50.1</b>	3.88	3.38	<b>48.2</b>
<i>Blood-based biomarkers</i>						
HDL (mmol/L)	1.58	1.50	<b>16.8</b>	1.57	1.54	<b>6.6</b>
CRP (mg/L)	1.88	2.59	<b>-37.3</b>	1.92	2.75	<b>-42.5</b>
HbA1c (mmol/mol)	36.5	39.4	<b>-42.3</b>	36.8	38.7	<b>-28.7</b>
DHEAS ( $\mu\text{mol/L}$ )	4.69	3.46	<b>40.0</b>	4.55	3.71	<b>27.2</b>
EGFR	91.6	82.6	<b>49.1</b>	90.6	85.1	<b>29.5</b>
Hgb (g/L)	137.3	135.3	<b>14.8</b>	137.1	133.1	<b>29.6</b>
Albumin (g/L)	47.1	45.9	<b>42.8</b>	47.0	45.8	<b>40.7</b>
<i>Systematic risk scores</i>						
Allostatic load	-0.17	2.63	<b>-69.1</b>	-0.11	1.59	<b>-41.4</b>
CVD risk score	-0.19	1.72	<b>-59.3</b>	0.03	1.05	<b>-34.2</b>

Notes: Crude effect size is the difference in the mean biomarker/risk score values by disability status, expressed as percentage of the standard deviation of the biomarker/risk score; the lowest (zero) and highest (3+) groups are used in the case of the “number of difficulties” disability measure. Bold type indicates statistical significance at the 1% level (bootstrap with 500 replications). A negative effect size indicates that the biomarker/risk score has a higher mean value for the more disabled group.

Table S5: Definitions and summary statistics of covariates

Covariate	<i>Sample of origin</i> <sup>§</sup>			
	UKHLS		UKHLS&BHPS	
	Mean	s.d.	Mean	s.d.
<i>Self-assessed health</i>				
1 = respondent reports excellent health	0.13	0.34	0.15	0.35
2 = respondent reports very good health	0.39	0.49	0.39	0.49
3 = respondent reports good health	0.34	0.47	0.33	0.46
4 = respondent reports fair or poor health	0.14	0.34	0.14	0.35
<i>Socio-economic status</i>				
Degree = 1 if respondent has degree/equivalent	0.38	0.49	0.37	0.49
A-level = 1 if respondent has A-level/equivalent	0.19	0.39	0.20	0.40
O-level = 1 if respondent has O-level/basic qualification	0.31	0.46	0.31	0.46
No qualification = 1 if no qualifications reported	0.12	0.32	0.11	0.32
Homeowner=1 if respondent lives in owner-occupied property	0.79	0.41	0.79	0.41
Non-homeowner=1 if not in a owner-occupied property	0.21	0.41	0.21	0.41
Pre-disability benefits equivalised household income (log)	7.31	0.60	7.31	0.60
<i>Marital status and household structure</i>				
Single=1 if respondent is single	0.14	0.35	0.15	0.35
Married=1 if respondent is married/cohabitating	0.70	0.46	0.71	0.46
Sep/Div=1 if respondent is separated/divorced	0.09	0.29	0.09	0.28
Widowed=1 if respondent is widowed	0.06	0.24	0.06	0.24
Number of household members	2.66	1.25	2.69	1.26
Number of children in the household	0.53	0.91	0.54	0.91
<i>Residential region and urbanization level</i>				
England=1 if region is England	0.93	0.26	0.85	0.36
Wales=1 if region is Wales	0.03	0.16	0.07	0.26
Scotland=1 if region is Scotland	0.05	0.21	0.08	0.27
Urban=1 if urban area	0.75	0.43	0.74	0.44
Rural=1 if rural area	0.25	0.43	0.26	0.44
<i>Other personal characteristics</i>				
Male=1 if respondent is male	0.43	0.50	0.44	0.50
Female=1 if respondent is female	0.57	0.50	0.56	0.50
Age of respondent (years)	50.40	16.93	50.10	16.96
Light smoker=1 if smokes < 9 cigarettes/day	0.05	0.23	0.05	0.23
Moderate smoker=1 if smokes 10-19 cigarettes/day	0.08	0.27	0.08	0.27
Heavy smoker=1 if smokes 20+ cigarettes/day	0.04	0.20	0.04	0.20
Ex-smoker=1 if ex-smoker	0.36	0.48	0.35	0.47
Never smoker=1 if never smoked cigarettes	0.47	0.50	0.48	0.50
Maximum possible sample size	10,744		14,247	

<sup>§</sup> Sample size corresponds to the maximum possible sample size for the case of the UKHLS sample members or the combined BHPS and UKHLS sample. Sample size varies in the main text tables depending on the biomarker and the disability measure considered.

Table S6: Two and three years ahead prediction models: % impact of nurse-collected biomarkers on mean disability prevalence.

Marker	SAH	No. of functional difficulties reported			Mobility difficulty	Benefit receipt
		1 or more <sup>§</sup>	2 or more <sup>†</sup>	3 or more <sup>†</sup>		
<i>Prediction horizon t = 2</i>						
Waist/height ratio	excluded	18.5***	22.3***	26.0***	32.2***	32.0***
	included	8.8***	10.3***	12.0***	19.8***	21.3***
Grip Strength	excluded	-17.8***	-23.5***	-27.4***	-30.7***	-46.5***
	included	-14.2***	-18.2***	-21.1***	-18.7***	-34.0***
Hypertension <sup>‡</sup>	excluded	8.2	8.2	9.6	5.9	25.5*
	included	-1.0	-3.4	-4.0	-6.0	13.5
Heart rate	excluded	9.6***	13.2***	14.3***	8.0**	22.7***
	included	5.3*	8.1**	7.0**	3.5	19.4***
FVC <sup>1</sup>	excluded	-20.3***	-20.6***	-23.3***	-31.9***	-26.6***
	included	-8.6*	-8.0*	-9.0*	-13.5**	-12.3
FVC <sup>2</sup>	excluded	-20.0***	-20.4***	-23.0***	-30.3***	-25.0***
	included	-8.5*	-7.9*	-8.9**	-12.5*	-11.3
Mean $D_2$		0.107	0.046	0.020	0.057	0.028
<i>Prediction horizon t = 3</i>						
Waist/height ratio	excluded	21.0***	24.6***	28.5***	35.6***	30.5***
	included	12.0***	13.4***	15.5***	24.3***	19.1***
Grip Strength	excluded	-18.9***	-27.2***	-31.2***	-33.2***	-50.4***
	included	-15.6***	-23.0***	-26.3***	-25.3***	-39.4***
Hypertension <sup>‡</sup>	excluded	23.2***	26.7***	31.0***	23.3***	32.2***
	included	13.0**	14.7*	17.0*	10.9	19.7*
Heart rate	excluded	10.8***	12.1***	15.4***	6.3*	14.7***
	included	6.8**	6.7**	9.4**	1.8	10.4**
FVC <sup>1</sup>	excluded	-16.8***	-15.5***	-17.4***	-29.3***	-24.8***
	included	-5.3	-3.0	-3.6	-12.9*	-10.2
FVC <sup>2</sup>	excluded	-16.1***	-15.2***	-17.0***	-27.7***	-23.5***
	included	-4.9	-3.1	-3.4	-12.1*	-9.5
Mean $D_3$		0.116	0.051	0.024	0.065	0.031

<sup>1</sup> Without smoking covariate; <sup>2</sup> with smoking covariate; <sup>‡</sup> impact of switch from hypertensive to non-hypertensive

<sup>§</sup> Derived from binary probit model; <sup>†</sup> derived from ordered probit model

Statistical significance: \* = 10%, \*\* = 5%, \*\*\* = 1%.

Table S7: Two and three year ahead prediction models: % impact of blood-based biomarkers on mean disability prevalence.

Marker	SAH	No. of functional difficulties reported			Mobility difficulty	Benefit receipt
		1 or more <sup>§</sup>	2 or more <sup>†</sup>	3 or more <sup>†</sup>		
<i>Prediction horizon t = 2</i>						
HDL	excluded	-9.9***	-12.8**	-13.9**	-19.9***	-10.2*
	included	-4.6	-6.1	-6.5	-12.6***	-3.6
CRP	excluded	6.2**	8.1**	8.7**	12.8***	14.3***
	included	1.8	2.8	3.0	6.8*	9.4**
HbA1c	excluded	8.7***	9.5***	10.1***	13.2***	11.5*
	included	3.6	3.3	3.5	6.4*	7.4
DHEAS	excluded	-16.4***	-18.6***	-20.2***	-13.4**	-16.7*
	included	-13.7***	-14.9***	-16.0***	-8.4	-10.0
EGFR	excluded	0.0	-2.0	-2.3	-5.4	2.2
	included	1.1	-1.0	-1.0	-2.5	3.9
Hgb	excluded	-10.7*	-12.2**	-12.9**	-12.3**	-2.0
	included	-9.7*	-10.6**	-11.1**	-9.7**	0.5
Albumin	excluded	-15.0***	-19.0***	-21.4***	-19.3***	-11.7**
	included	-11.6***	-15.3***	-16.3***	-14.2***	-7.3
Mean $D_2$		0.107	0.046	0.020	0.057	0.028
<i>Prediction horizon t = 3</i>						
HDL	excluded	-10.5***	-12.0***	-13.8***	-17.8***	-16.0**
	included	-5.5	-5.8	-6.7	-11.40**	-9.8
CRP	excluded	14.3***	16.7***	18.9***	20.0***	11.3**
	included	10.4***	12.0***	13.7***	12.5***	6.4
HbA1c	excluded	10.4***	11.6***	13.3***	11.9***	5.8
	included	5.4*	5.5	6.5	5.2	0.2
DHEAS	excluded	-10.7**	-12.8**	-14.6**	-8.2	-25.5***
	included	-9.1*	-11.0**	-12.5**	-3.8	-18.3**
EGFR	excluded	-8.7*	-11.5**	-13.3**	-4.4	5.9
	included	-7.4	-2.0*	-11.2*	-1.7	7.4
Hgb	excluded	-6.9	-8.3*	-9.4*	-9.3*	-13.3**
	included	-5.9	-7.0	-7.6	-6.6	-10.3
Albumin	excluded	-8.2**	-10.0**	-11.3**	-12.9***	-13.2**
	included	-5.5	-6.7	-7.5	-8.4*	-9.1
Mean $D_3$		0.116	0.051	0.024	0.065	0.031

<sup>§</sup> Derived from binary probit model; <sup>†</sup> derived from ordered probit model  
Statistical significance: \* = 10%, \*\* = 5%, \*\*\* = 1%.

Table S8: Two and three year ahead prediction models: % impact of systematic risk scores on mean disability prevalence.

Marker	SAH	No. of functional difficulties reported			Mobility difficulty	Benefit receipt
		1 or more <sup>§</sup>	2 or more <sup>†</sup>	3 or more <sup>†</sup>		
<i>Prediction horizon t = 2</i>						
Allostatic load	excluded	16.9***	22.7***	23.0***	22.9***	23.7***
	included	7.8*	10.9**	11.5**	12.8***	16.8**
CVD risk	excluded	10.1**	13.4***	14.2***	16.2***	18.7***
	included	2.5	4.2	4.0	7.4	13.2*
Mean $D_2$		0.107	0.046	0.020	0.057	0.028
<i>Prediction horizon t = 3</i>						
Allostatic load	excluded	20.0***	24.7***	27.5***	32.1***	16.8***
	included	12.1***	15.0***	16.7***	20.7***	7.0
CVD risk	excluded	17.1***	20.6***	23.0***	26.8***	8.3
	included	10.4***	12.4**	13.8***	17.3***	-0.3
Mean $D_3$		0.116	0.051	0.024	0.065	0.031

<sup>§</sup> Derived from binary probit model; <sup>†</sup> derived from ordered probit model  
Statistical significance: \* = 10%, \*\* = 5%, \*\*\* = 1%.

Table S9: Estimated mean partial impacts of deterioration in SAH (“excellent” to “poor/very poor”) and biomarkers (3-standard deviation change centred on mean) on disability prevalence 4 years ahead

Health indicator	No. of functional difficulties reported			Mobility difficulty	Benefit receipt
	1 or more <sup>§</sup>	2 or more <sup>†</sup>	3 or more <sup>†</sup>		
SAH	0.208	0.118	0.061	0.129	0.076
WHR	0.042	0.024	0.012	0.057	0.026
SAH	0.213	0.121	0.063	0.135	0.078
Grip strength	0.039	0.027	0.014	0.022	0.028
SAH	0.225	0.127	0.064	0.152	0.088
Hypertension*	0.004	0.003	0.001	0.009	0.005
SAH	0.221	0.125	0.063	0.152	0.086
HR	0.038	0.022	0.010	0.026	0.017
SAH	0.202	0.114	0.056	0.124	0.086
FVC	0.056	0.026	0.012	0.036	0.027
SAH	0.219	0.125	0.064	0.160	0.080
HDL	0.059	0.028	0.014	0.032	0.002
SAH	0.215	0.120	0.060	0.158	0.076
CRP	0.036	0.016	0.010	0.024	0.015
SAH	0.211	0.120	0.061	0.158	0.076
HbA1c	0.042	0.019	0.009	0.015	0.004
SAH	0.224	0.128	0.065	0.167	0.080
DHEAS	0.034	0.015	0.008	0.015	0.004
SAH	0.228	0.129	0.066	0.167	0.080
EGFR	0.028	0.015	0.007	0.025	0.006
SAH	0.216	0.123	0.063	0.160	0.075
Hgb	0.013	0.006	0.003	0.015	0.017
SAH	0.228	0.129	0.066	0.165	0.078
Albumin	0.030	0.018	0.008	0.031	0.014
SAH	0.184	0.104	0.050	0.139	0.072
Allostatic load	0.069	0.033	0.015	0.056	0.016
SAH	0.196	0.110	0.052	0.143	0.073
CVD risk	0.051	0.025	0.011	0.049	0.015

<sup>§</sup> derived from binary probit model. <sup>†</sup> derived from ordered probit model. \* Impact of switch from non-hypertensive to hypertensive. Statistical significance: all SAH effects significant at 1% level; for statistical significance of biomarkers, see Table 1 of the paper

Table S10: Estimated mean partial impacts of deterioration in SAH (“excellent” to “poor/very poor”) and biomarkers (3-standard deviation change centred on mean) on disability prevalence 4 years ahead: models estimated after excluding individuals who were given feedback about elevated blood pressure.

Health indicator	No. of functional difficulties reported			Mobility difficulty	Benefit receipt
	1 or more <sup>§</sup>	2 or more <sup>†</sup>	3 or more <sup>†</sup>		
SAH	0.202	0.114	0.057	0.116	0.082
WHR	0.035	0.017	0.009	0.050	0.021
SAH	0.205	0.115	0.058	0.121	0.079
Grip Strength	0.048	0.037	0.016	0.021	0.027
SAH	0.206	0.115	0.058	0.137	0.089
Heart rate	0.039	0.020	0.011	0.032	0.016
SAH	0.192	0.105	0.051	0.110	0.088
FVC	0.055	0.026	0.012	0.033	0.032
SAH	0.209	0.121	0.060	0.142	0.090
HDL	0.052	0.026	0.013	0.028	0.005
SAH	0.212	0.120	0.058	0.136	0.087
CRP	0.049	0.021	0.010	0.033	0.012
SAH	0.195	0.110	0.055	0.134	0.083
HbA1c	0.044	0.020	0.010	0.016	0.001
SAH	0.215	0.124	0.062	0.144	0.090
DHEAS	0.043	0.018	0.009	0.019	0.005
SAH	0.220	0.126	0.063	0.144	0.090
eGFR	0.026	0.014	0.007	0.026	0.003
SAH	0.201	0.113	0.057	0.135	0.082
Hgb	0.006	0.005	0.003	0.017	0.018
SAH	0.220	0.125	0.063	0.144	0.089
Albumin	0.018	0.011	0.005	0.024	0.008
SAH	0.169	0.094	0.044	0.119	0.079
Allostatic load	0.064	0.031	0.015	0.057	0.012
SAH	0.182	0.100	0.047	0.124	0.081
CVD risk	0.056	0.030	0.012	0.046	0.013

<sup>§</sup> derived from binary probit model. <sup>†</sup> derived from ordered probit model. \* Impact of switch from non-hypertensive to hypertensive.

## Algebraic structure of the LV model

The equation for latent general health is:

$$h_{i0} = \alpha X_{i0} + \eta_{i0} \quad (1)$$

where  $X_{i0}$  is a set of covariates, observed at the time of biomarker measurement, representing the observable determinants of the initial health state and  $\eta_{i0}$  is an independent random error that captures the remaining unobservable influences. Observed SAH is a noisy indicator, related to  $h_{i0}$  by a measurement equation:

$$S_{i0} = L(\beta_0 + \beta_1 h_{i0} + v_{i0}) \quad (2)$$

where the unobserved random variable  $u_{i0}$  captures the measurement noise in SAH and  $L(\cdot)$  is the ordinal probit link function. We use a set of 12 biomarkers,  $B_{1i0} \dots B_{12i0}$ , which are also noisy measures. It is possible that, in addition to  $h_{i0}$ , the measured biomarkers reflect some further dimension of health,  $b_{i0}$ , to which SAH is insensitive. To allow for this, we specify further latent health and measurement equations:

$$b_{i0} = \gamma X_{i0} + \lambda_{i0} \quad (3)$$

$$B_{ji0} = \delta_{j0} + \delta_{j1} h_{i0} + \delta_{j2} b_{i0} + w_{ji0}, \quad j = 1 \dots 12 \quad (4)$$

where  $\lambda_{i0}$  is a random error, and  $w_{jit}$  captures the measurement noise in biomarker  $j$ . The random residuals for the two dimensions of latent health are independent. In this Gaussian distributional setting, there is no loss of generality in specifying a triangular system with  $S_{i0}$  measuring only  $h_{i0}$  and  $B_{i0}$  reflecting both  $h_{i0}$  and  $b_{i0}$ , with  $h_{i0}$  and  $b_{i0}$  conditionally independent. Any bivariate Gaussian distribution can be represented in that way, and it is a convenient representation for our purpose of assessing the additional informational content of the biomarker additional to SAH.

The three observed disability outcomes are related to latent health and we allow the

covariates  $X_{i0}$  also to influence disability directly:

$$D_{it} = L^D (\theta_{0t} + \theta_{1t}h_{i0} + \theta_{2t}b_{i0} + \theta_{3t}X_{i0} + \theta_{4t}u_i + \varepsilon_{it}) , \quad t = 2, 3, 4 \quad (5)$$

where  $u_i$  is an unobserved random effect whose effect may vary with  $t$ ;  $\varepsilon_{i2} \dots w_{i4}$  are random errors distributed independently of  $u_i, \eta_{i0}, \lambda_{i0}, v_{i0}, w_{i0}$ , which are themselves mutually independent. For the purposes of estimation we resolve the inherent indeterminacy caused by non-observability of the latent variables by normalising at 1.0 the loadings of  $h_{i0}$  and  $b_{i0}$  on SAH and hypertension respectively, and of  $u_i$  on disability at the 4-year horizon. The complete system (1)-(5) is estimated jointly by maximum likelihood. Full parameter estimates are given in the appendix.