

## Supplementary Material

### Levels of Ankle-Brachial Index and the Risk of Diabetes Mellitus Complications

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## Supplemental Methods

### Imputation Models

The imputation models included the following variables: age, sex, ABI, smoking status, weight, height, natural logarithm (ln) of systolic BP, ln(pulse pressure), ln(total serum cholesterol), ln(LDL cholesterol), ln(HDL cholesterol), ln(triglycerides), HbA1c, ln(glucose), diabetes duration, comorbidities (hypertension, atrial fibrillation, heart failure, COPD, nephropathy, retinopathy, neuropathy, malignant neoplasms, dyslipidaemia, arthritis, asthma, hypothyroidism, acute myocardial infarction, angina, transient ischemic attack, stroke), and medications (antidiabetic therapy, diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system, other antihypertensives, statins, other lipid modifying agents, aspirin, systemic corticosteroids, psycholeptics, and psychoanaleptics). The censoring indicator and the Nelson-Aalen estimate of the cumulative hazard function for the time to cardiovascular disease were also included.[1] Some variables were ln transformed to avoid the unlikely possibility of imputing any negative numbers, and converted back to their original scale after imputation.

### Supplemental Tables

Supplemental Table S1. Missing Counts and Comparison of Baseline Characteristics Between Imputed Data and Complete Cases

Variable	Missing Counts	Imputed Dataset (n = 34689)	Complete Cases (n = 18196)
Age, years	-	66.23 (10.47)	66.53 (10.18)
Men	-	17880 (51.5%)	9232 (50.7%)
Smoking habit	-	8003 (23.1%)	4191 (23.0%)
BMI, kg/m <sup>2</sup>	26.7%	30.38 (5.00)	30.32 (4.81)
Systolic BP, mmHg	9.0%	136.17 (15.78)	135.87 (15.41)
Diastolic BP, mmHg	9.0%	77.15 (9.51)	76.90 (9.34)
Pulse Pressure, mmHg	9.0%	59.02 (14.44)	58.97 (14.15)
Total Cholesterol, mmol/l	20.9%	5.06 (0.99)	5.04 (0.93)
LDL Cholesterol, mmol/l	27.3%	2.96 (0.85)	2.94 (0.79)
HDL Cholesterol, mmol/l	26.6%	1.36 (0.42)	1.33 (0.34)
Triglycerides, mmol/l	24.5%	1.73 (1.09)	1.69 (0.97)
HbA1c, mmol/mol	24.9%	54.91 (17.09)	54.71 (16.48)
HbA1c, %	24.9%	7.17 (1.56)	7.16 (1.51)
Glucose, mmol/l	19.5%	8.33 (2.76)	8.27 (2.69)
Diabetes duration	-	5.76 (5.66)	5.80 (5.54)
Comorbidities			
Hypertension	-	23554 (67.9%)	12706 (69.8%)
Atrial fibrillation	-	1673 (4.8%)	846 (4.6%)

Variable	Missing Counts	Imputed Dataset (n = 34689)	Complete Cases (n = 18196)
Heart failure	-	841 (2.4%)	423 (2.3%)
COPD	-	3161 (9.1%)	1614 (8.9%)
Malignant neoplasms	-	2743 (7.9%)	1382 (7.6%)
Dyslipidaemia	-	17914 (51.6%)	10031 (55.1%)
Arthritis	-	284 (0.8%)	123 (0.7%)
Asthma	-	1433 (4.1%)	760 (4.2%)
Hypothyroidism	-	2064 (6.0%)	1102 (6.1%)
Complications of diabetes			
Nephropathy	-	1918 (5.5%)	1011 (5.6%)
Retinopathy	-	682 (2.0%)	355 (2.0%)
Neuropathy	-	291 (0.8%)	136 (0.7%)
Medication			
Antidiabetic therapy	-	27259 (78.6%)	14731 (81.0%)
Diuretics	-	8244 (23.8%)	4416 (24.3%)
Beta-blockers	-	4325 (12.5%)	2312 (12.7%)
Calcium channel blockers	-	5891 (17.0%)	3248 (17.9%)
Agents acting on the renin-angiotensin system	-	20046 (57.8%)	11008 (60.5%)
Other antihypertensives	-	1648 (4.8%)	850 (4.7%)
Statins	-	15518 (44.7%)	8894 (48.9%)
Other lipid-lowering agent	-	2364 (6.8%)	1237 (6.8%)
Aspirin	-	9716 (28.0%)	5397 (29.7%)
Systemic corticosteroids	-		
Psycholeptics	-		
Psychoanaleptics	-		

Values are presented as mean (SD) or N(%).

ABI indicates ankle brachial index; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin A; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of participants.

Supplemental Table S2. Variables of adjustment used in the Cox proportional hazard models

<b>Outcome</b>	<b>Adjusting variables</b>
AMI	Age, BMI, HDL Cholesterol, LDL Cholesterol, Total Cholesterol, HbA1c, Sex, Aspirin, Calcium channel blockers, Antidiabetic therapy, Smoking habit, Pulse Pressure, Systolic BP, Triglycerides
Ischemic stroke	Age, LDL Cholesterol, Total Cholesterol, HbA1c, Sex, Atrial fibrillation, Antidiabetic therapy, Smoking habit, Systolic BP
MCE *	Age, BMI, LDL Cholesterol, Total Cholesterol, Glucose, HbA1c, Sex, Atrial fibrillation, Aspirin, Calcium channel blockers, Chronic kidney disease, Antidiabetic therapy, Smoking habit, Systolic BP, Triglycerides
Mortality †	Age, BMI, HDL Cholesterol, Total Cholesterol, Diastolic BP, HbA1c, Sex, Atrial fibrillation, Diuretics, Beta-blockers, Chronic kidney disease, COPD, Malignant neoplasms, Smoking habit, Statins
Nephropathy	Age, BMI, LDL Cholesterol, Glucose, HbA1c, Sex, Atrial fibrillation, Other antihypertensives, Diuretics, Beta-blockers, Calcium channel blockers, Agents acting on the renin-angiotensin system, Other lipid-lowering agent, Antidiabetic therapy, Hypertension, Smoking habit, Pulse Pressure, Triglycerides, Diabetes duration
Retinopathy	LDL Cholesterol, Total Cholesterol, HbA1c, Aspirin, Chronic kidney disease, Antidiabetic therapy, Pulse Pressure, Diabetes duration
Neuropathy	LDL Cholesterol, HbA1c, Aspirin, Chronic kidney disease, COPD, Antidiabetic therapy, Smoking habit, Pulse Pressure, Diabetes duration

\* A composite of AMI and ischemic stroke.

† All-cause mortality.

AMI indicates acute myocardial infarction; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin A; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Supplemental Table S3. Baseline Characteristics of the Study Population. Complete Cases

Variable	0.4 ≤ ABI < 0.5 n = 56	0.5 ≤ ABI < 0.7 n = 450	0.7 ≤ ABI < 0.9 n = 2091	0.9 ≤ ABI < 1.1 n = 10486	1.1 ≤ ABI < 1.3 n = 4098	1.3 ≤ ABI < 3 n = 1015
Age, years	70.44 (9.63)	70.33 (9.55)	67.71 (10.00)	66.39 (10.22)	65.32 (10.05)	68.42 (9.92)
Men	35 (62.5%)	282 (62.7%)	1127 (53.9%)	5060 (48.3%)	2172 (53.0%)	556 (54.8%)
Smoking habit	21 (37.5%)	155 (34.4%)	576 (27.5%)	2385 (22.7%)	857 (20.9%)	197 (19.4%)
BMI, kg/m <sup>2</sup>	29.58 (5.41)	29.51 (4.83)	30.51 (4.91)	30.29 (4.79)	30.34 (4.73)	30.51 (5.08)
Systolic BP, mmHg	140.43 (17.22)	139.88 (17.20)	137.90 (16.77)	135.40 (14.99)	135.63 (15.13)	135.47 (16.32)
Diastolic BP, mmHg	74.21 (9.51)	74.72 (9.79)	76.39 (9.62)	76.87 (9.26)	77.63 (9.21)	76.38 (9.61)
Pulse Pressure, mmHg	66.21 (13.44)	65.16 (16.48)	61.51 (15.44)	58.53 (13.72)	58.00 (13.85)	59.09 (14.60)
Total Cholesterol, mmol/l	5.15 (0.85)	5.07 (0.96)	5.08 (0.96)	5.05 (0.94)	5.03 (0.91)	4.95 (0.86)
LDL Cholesterol, mmol/l	3.05 (0.84)	2.98 (0.85)	2.99 (0.80)	2.94 (0.79)	2.93 (0.79)	2.86 (0.76)
HDL Cholesterol, mmol/l	1.24 (0.37)	1.30 (0.34)	1.31 (0.33)	1.34 (0.34)	1.34 (0.35)	1.36 (0.36)
Triglycerides, mmol/l	1.91 (1.02)	1.74 (0.91)	1.73 (0.99)	1.70 (0.98)	1.67 (0.96)	1.62 (0.92)
HbA1c, mmol/mol	55.76 (15.15)	57.95 (18.12)	56.03 (17.22)	54.45 (16.42)	54.27 (16.31)	54.88 (15.25)
HbA1c, %	7.25 (1.39)	7.45 (1.66)	7.28 (1.58)	7.13 (1.50)	7.12 (1.49)	7.17 (1.40)
Glucose, mmol/l	8.03 (2.48)	8.42 (2.74)	8.46 (2.94)	8.24 (2.66)	8.26 (2.62)	8.18 (2.58)
Diabetes duration	6.37 (5.00)	6.72 (5.52)	6.32 (5.98)	5.73 (5.51)	5.50 (5.28)	6.31 (5.83)
Comorbidities						

Variable	0.4 ≤ ABI < 0.5 n = 56	0.5 ≤ ABI < 0.7 n = 450	0.7 ≤ ABI < 0.9 n = 2091	0.9 ≤ ABI < 1.1 n = 10486	1.1 ≤ ABI < 1.3 n = 4098	1.3 ≤ ABI < 3 n = 1015
Hypertension	40 (71.4%)	340 (75.6%)	1559 (74.6%)	7282 (69.4%)	2739 (66.8%)	746 (73.5%)
Atrial fibrillation	2 (3.6%)	29 (6.4%)	125 (6.0%)	461 (4.4%)	159 (3.9%)	70 (6.9%)
Heart failure	4 (7.1%)	10 (2.2%)	72 (3.4%)	218 (2.1%)	83 (2.0%)	36 (3.5%)
COPD	10 (17.9%)	68 (15.1%)	246 (11.8%)	913 (8.7%)	283 (6.9%)	94 (9.3%)
Malignant neoplasms	7 (12.5%)	39 (8.7%)	155 (7.4%)	809 (7.7%)	302 (7.4%)	70 (6.9%)
Complications of diabetes						
Nephropathy	7 (12.5%)	42 (9.3%)	132 (6.3%)	587 (5.6%)	178 (4.3%)	65 (6.4%)
Retinopathy	4 (7.1%)	17 (3.8%)	46 (2.2%)	197 (1.9%)	68 (1.7%)	23 (2.3%)
Neuropathy	2 (3.6%)	11 (2.4%)	20 (1.0%)	62 (0.6%)	28 (0.7%)	13 (1.3%)
Medication						
Antidiabetic therapy	44 (78.6%)	387 (86.0%)	1734 (82.9%)	8428 (80.4%)	3291 (80.3%)	847 (83.4%)
Diuretics	21 (37.5%)	137 (30.4%)	555 (26.5%)	2571 (24.5%)	881 (21.5%)	251 (24.7%)
Beta-blockers	6 (10.7%)	64 (14.2%)	298 (14.3%)	1338 (12.8%)	471 (11.5%)	135 (13.3%)
Calcium channel blockers	16 (28.6%)	109 (24.2%)	408 (19.5%)	1843 (17.6%)	676 (16.5%)	196 (19.3%)
Agents acting on the renin-angiotensin system	38 (67.9%)	317 (70.4%)	1381 (66.0%)	6292 (60.0%)	2341 (57.1%)	639 (63.0%)
Other antihypertensives	4 (7.1%)	35 (7.8%)	117 (5.6%)	454 (4.3%)	186 (4.5%)	54 (5.3%)

Variable	0.4 ≤ ABI < 0.5 n = 56	0.5 ≤ ABI < 0.7 n = 450	0.7 ≤ ABI < 0.9 n = 2091	0.9 ≤ ABI < 1.1 n = 10486	1.1 ≤ ABI < 1.3 n = 4098	1.3 ≤ ABI < 3 n = 1015
Statins	28 (50.0%)	259 (57.6%)	1051 (50.3%)	5177 (49.4%)	1925 (47.0%)	454 (44.7%)
Other lipid-lowering agent	6 (10.7%)	38 (8.4%)	129 (6.2%)	760 (7.2%)	247 (6.0%)	57 (5.6%)
Aspirin	17 (30.4%)	180 (40.0%)	705 (33.7%)	3020 (28.8%)	1140 (27.8%)	335 (33.0%)

Values are presented as mean (SD) or n(%).

ABI indicates ankle brachial index; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin A; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of participants.



Supplemental Table S4. Events and Incidence Rate\* (95% Confidence Interval) for the Outcomes by Ankle Brachial Index Categories. Complete Cases

		0.4 ≤ ABI < 0.5		0.5 ≤ ABI < 0.7		0.7 ≤ ABI < 0.9		0.9 ≤ ABI < 1.1		1.1 ≤ ABI < 1.3		1.3 ≤ ABI	
Cardiovascular													
AMI	1	3.6 (0.5, 25.6)	23	9.7 (6.4, 14.5)	68	5.7 (4.5, 7.2)	265	4.3 (3.8, 4.8)	93	3.7 (3.0, 4.6)	30	5.0 (3.5, 7.1)	
Ischemic stroke	4	15.0 (5.6, 39.9)	52	22.6 (17.2, 29.6)	129	10.9 (9.2, 13.0)	535	8.8 (8.0, 9.5)	172	7.0 (6.0, 8.1)	71	12.0 (9.5, 15.1)	
MCE †	5	18.9 (7.9, 45.5)	71	31.5 (24.9, 39.7)	195	16.7 (14.5, 19.2)	774	12.8 (11.9, 13.7)	259	10.6 (9.4, 11.9)	96	16.4 (13.4, 20.0)	
Mortality ‡	17	60.5 (37.6, 97.3)	112	46.1 (38.3, 55.4)	280	23.0 (20.5, 25.9)	1060	17.0 (16.0, 18.0)	349	13.9 (12.5, 15.4)	157	25.7 (21.9, 30.0)	
Nephropathy	13	60.2 (34.9, 103.6)	102	52.0 (42.8, 63.1)	354	33.5 (30.2, 37.2)	1439	26.0 (24.6, 27.3)	552	24.3 (22.4, 26.4)	167	31.2 (26.8, 36.3)	
Retinopathy	4	16.3 (6.1, 43.4)	41	18.4 (13.6, 25.0)	105	9.0 (7.5, 11.0)	346	5.7 (5.2, 6.4)	123	5.0 (4.2, 6.0)	52	8.9 (6.8, 11.7)	
Neuropathy	1	3.7 (0.5, 26.5)	28	12.1 (8.4, 17.6)	80	6.8 (5.4, 8.4)	225	3.7 (3.2, 4.2)	89	3.6 (2.9, 4.4)	24	4.0 (2.7, 6.0)	

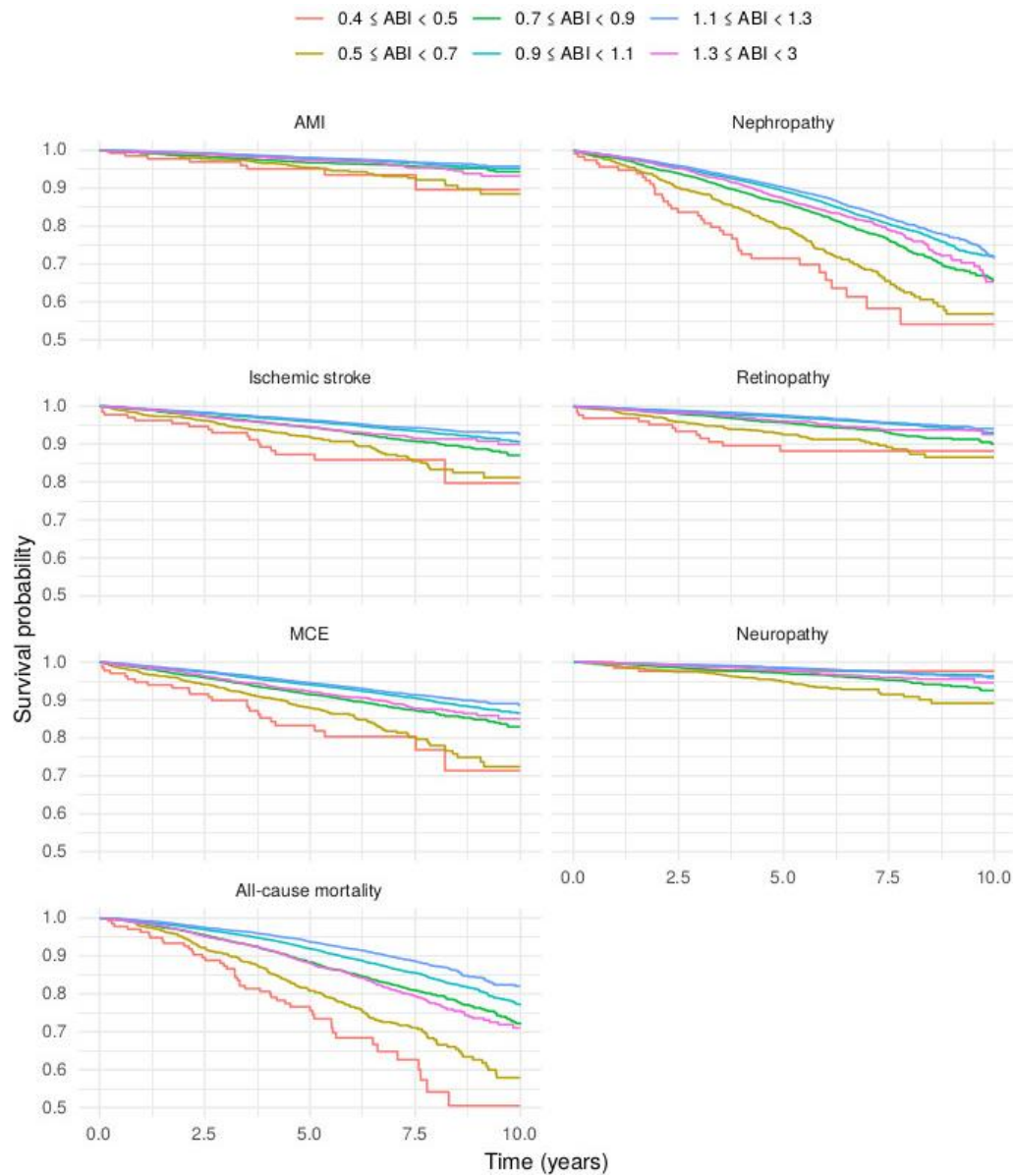
\* per 1000 person-years.

† A composite of AMI and ischemic stroke.

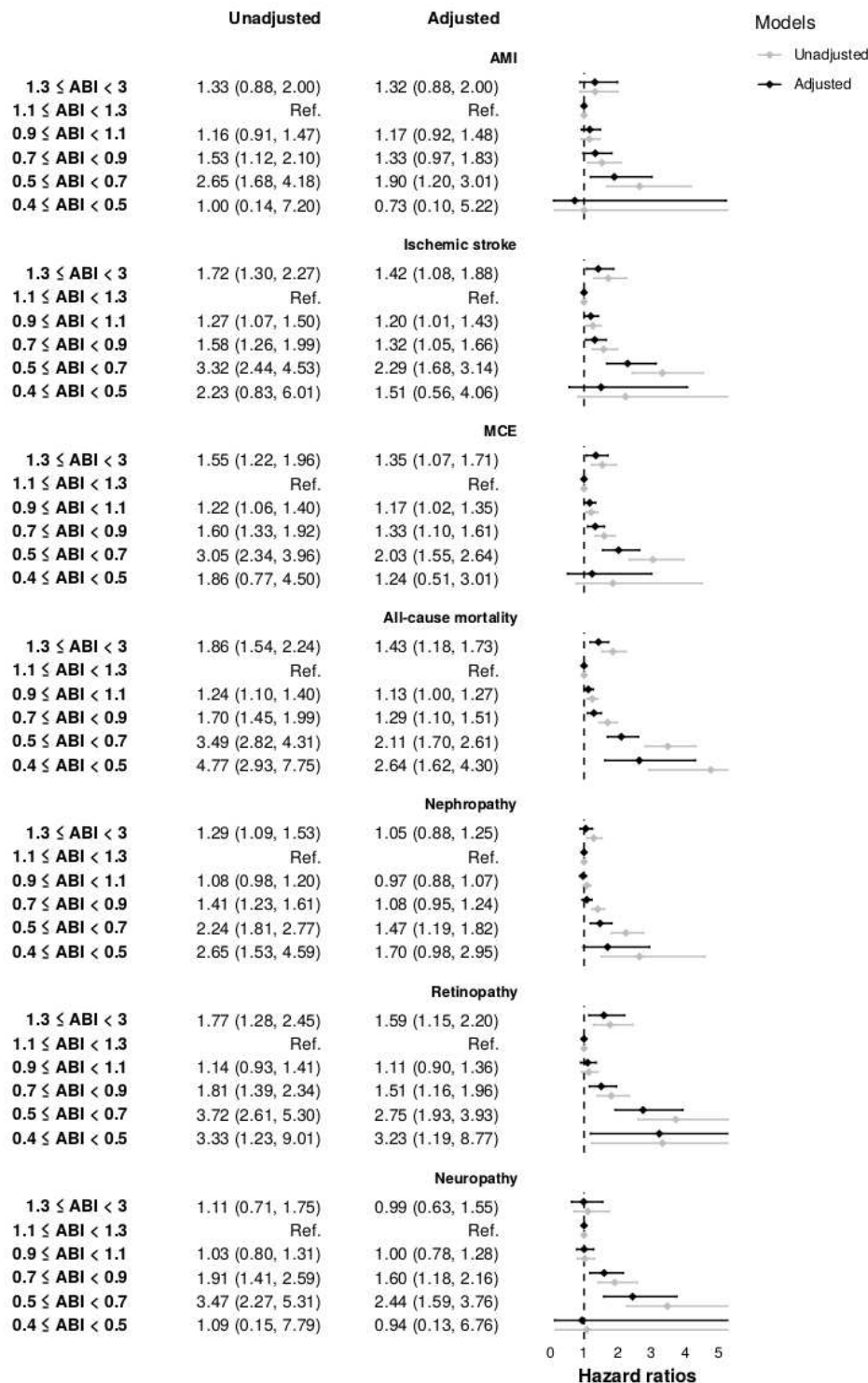
‡ All-cause mortality.

ABI indicates ankle brachial index; AMI, acute myocardial infarction; MCE, major cardiovascular event; n, number of participants.

## Supplemental Figures



Supplemental Figure S1. Kaplan-Meier curves for the study outcomes



Supplemental Figure S2. Hazard Ratios for Each Outcome by Ankle Brachial Index Categories. Complete Cases. ABI indicates ankle brachial index; AMI, acute myocardial infarction; MCE, major cardiovascular event.

## REFERENCES

1. White IR, Royston P, Wood AM (2011) Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 30(4):377–399. <https://doi.org/10.1002/sim.4067>