

Supplemental Table 1. Comparison of baseline characteristics of the total VHM&PP cohort and the VHM&PP study cohort for assessment of longitudinal GGT-Change, 1985-2005

	Males		Females	
	Cohort for assessment of longitudinal GGT-change	Total VHM&PP Cohort, 1985-2005	Cohort for assessment of longitudinal GGT-change	Total VHM&PP Cohort, 1985-2005
	(n=32,365)	(n=85,035)	(n=43,748)	(n=99,739)
Age, mean±SD (range), y	42.1±13.6 (18-89)	41.6±15.1 (18-96)	42.0±14.4 (19-90)	41.7±15.8 (18-95)
Body-mass-index, mean±SD (median), kg/m ²	25.3±3.4 (25.0)	25.4±3.7 (24.9)	24.1±4.3 (23.3)	24.2±4.6 (23.3)
Glucose, mean±SD (median), mg/dL	86.4±22.0 (84.0)	91.1±24.8 (87.0)	84.3±18.4 (83.0)	86.7±20.8 (84.0)
Triglycerides, mean±SD (median), mg/dL	152.4±105.4 (123.0)	148.8±106.9 (117.0)	111.4±64.9 (95.0)	111.4±67.6 (94.0)
Total Cholesterol, mean±SD (median), mg/dL	220.9±46.8 (218.0)	214.0±47.9 (210.0)	216.1±46.5 (211.0)	213.0±46.6 (208.0)
Gamma-glutamyltransferase, mean±SD (median), U/L	42.2±55.7 (28.6)	43.9±63.0 (28.6)	23.7±29.2 (17.9)	24.1±33.1 (17.9)
Systolic Blood Pressure, mean±SD (median), mm Hg	131.9±18.0 (130.0)	132.0±19.2 (130.0)	127.6±20.8 (125.0)	127.5±21.7 (124.0)
Diastolic Blood Pressure, mean±SD (median), mm Hg	81.8±10.7 (80.0)	81.5±10.9 (80.0)	79.3±11.0 (80.0)	79.0±11.2 (80.0)
Occupational status				
Blue collar - (%)	31.7	37.8	36.4	37.3
White collar - (%)	58.3	51.8	56.5	53.6
Self-employed - (%)	10.0	10.4	7.1	9.1
Current or Former Cigarette Smoking - (%)	31.5	29.6	23.4	20.0
Total Mortality - no (%)	2,304 (7.1)	7,391 (8.7)	2,247 (5.1)	6,817 (6.8)
Cardiovascular/cerebrovascular deaths - no. (%)	986 (3.0)	3063 (3.6)	969 (2.2)	3,709 (3.7)

All presented values are referring to baseline (i.e. measurement at first visit)

Supplemental Table 2. All-cause mortality and mortality from cardiovascular disease in male VHM&PP participants according to categories of longitudinal GGT-change after excluding participants with baseline GGT concentrations >60 U/L and/or an GGT increase into the abnormal range (>60 U/L), VHM&PP 1985-2005

	Longitudinal GGT-change							p for trend GGT decrease*	p for trend GGT increase*
	Decrease			Stable	Increase				
	Pronounced n=1850	Moderate n=4177	Mild n=4441		Mild n=4466	Moderate n=4231	Pronounced n=2455		
Longitudinal 7-year GGT-change (U/L) - Range	<(-7.99)	-7.98-(-3.03)	-3.02-(-0.69)	-0.68-1.26	1.27-3.76	3.77-9.16	>9.17		
Longitudinal 7-year GGT-change - mean±SD (median) (U/L)	-12.8±11.7 (-11.0)	-5.0±1.4 (-4.8)	-1.8±0.7 (-1.7)	0.3±0.6 (0.2)	2.4±0.7 (2.4)	5.9±1.5 (5.7)	15.1±5.9 (13.2)		
Baseline GGT - mean±SD (median) (U/L)	43.8±10.1 (44.8)	33.1±10.6 (32.2)	26.5±9.9 (25.1)	23.8±9.6 (21.5)	23.0±9.6 (21.5)	24.9±10.5 (23.3)	26.3±9.0 (25.1)		
ALL-CAUSE MORTALITY (n=1621)									
HR (95% CI)†	0.99 (0.80-1.22)	1.07 (0.90-1.26)	0.95 (0.80-1.13)	1.00 (Ref)	1.09 (0.91-1.31)	1.15 (0.95-1.39)	1.39 (1.12-1.72)	0.88	0.003
TOTAL CVD MORTALITY (n=700)									
HR (95% CI)†	0.95 (0.69-1.31)	1.00 (0.77-1.29)	0.96 (0.77-1.25)	1.00 (Ref)	1.11 (0.84-1.47)	1.26 (0.95-1.68)	1.36 (0.98-1.90)	0.89	0.027
CORONARY HEART DISEASE (n=384)									
HR (95% CI)†	0.96 (0.62-1.48)	0.99 (0.70-1.41)	0.99 (0.70-1.42)	1.00 (Ref)	1.14 (0.78-1.66)	1.35 (0.93-1.97)	1.03 (0.63-1.68)	0.93	0.29
CONGESTIVE HEART FAILURE (n=62)									
HR (95% CI)†	1.63 (0.62-4.33)	0.77 (0.30-2.00)	1.39 (0.60-3.24)	1.00 (Ref)	0.77 (0.27-2.19)	1.04 (0.37-2.93)	1.25 (0.39-4.11)	0.90	0.80
STROKE (n=157)									
HR (95% CI)†	0.85 (0.42-1.71)	1.11 (0.65-1.92)	0.76 (0.42-1.36)	1.00 (Ref)	1.04 (0.57-1.91)	1.35 (0.74-2.47)	1.98 (1.04-3.78)	0.98	0.025

*Log-linear trends across categories of increasing or decreasing GGT, in respect to stable GGT, were tested using the median GGT-change for each category as an ordinal variable in an extended Cox proportional hazards model adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and the period of GGT-change assessment. GGT and triglycerides were log-transformed.

†Estimated from extended Cox proportional hazards models adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and period of GGT-change assessment. GGT and triglycerides were log-transformed.

Supplemental Table 3. All-cause mortality and mortality from cardiovascular disease in female VHM&PP participants according to categories of longitudinal GGT-change after excluding female participants with baseline GGT concentrations >36 U/L and/or an GGT increase into the abnormal range (>36 U/L), VHM&PP 1985-2005

	Longitudinal GGT-change							p for trend GGT decrease*	p for trend GGT increase*
	Decrease			Stable	Increase				
	Pronounced n=3410	Moderate n=5923	Mild n=6078		Mild n=6080	Moderate n=5967	Pronounced n=3521		
Longitudinal 7-year GGT-change (U/L) - Range	<(-4.50)	-4.49-(-1.98)	-1.97-(-0.56)	-0.55-0.79	0.80-2.27	2.28-5.15	>5.15		
Longitudinal 7-year GGT-change - mean±SD (median) (U/L)	-7.6±4.9 (-6.4)	-3.0±0.7 (-3.0)	-1.2±0.4 (-1.2)	0.1±0.4 (0.0)	1.5±0.4 (1.4)	3.4±0.8 (3.3)	8.6±3.6 (7.5)		
Baseline GGT - mean±SD (median) (U/L)	25.2±6.4 (25.1)	19.7±5.9 (17.9)	17.1±5.2 (16.1)	15.9±5.4 (14.3)	15.2±5.4 (14.3)	15.3±5.9 (14.3)	16.1±5.5 (16.1)		
ALL-CAUSE MORTALITY (n=1591)									
HR (95% CI)†	1.08 (0.88-1.32)	1.02 (0.85-1.22)	0.95 (0.79-1.15)	1.00 (Ref)	1.00 (0.83-1.21)	1.16 (0.96-1.40)	1.28 (1.04-1.57)	0.38	0.005
TOTAL CVD MORTALITY (n=687)									
HR (95% CI)†	0.94 (0.69-1.28)	0.93 (0.71-1.21)	0.84 (0.63-1.14)	1.00 (Ref)	1.01 (0.76-1.34)	1.14 (0.86-1.51)	1.25 (0.91-1.71)	0.88	0.11
CORONARY HEART DISEASE (n=314)									
HR (95% CI)†	1.04 (0.65-1.67)	1.22 (0.81-1.83)	0.73 (0.46-1.17)	1.00 (Ref)	1.14 (0.74-1.76)	1.27 (0.82-1.96)	1.80 (1.15-2.81)	0.45	0.008
CONGESTIVE HEART FAILURE (n=72)									
HR (95% CI)†	0.87 (0.36-2.10)	0.59 (0.25-1.38)	0.90 (0.40-2.01)	1.00 (Ref)	0.78 (0.33-1.86)	0.95 (0.40-2.25)	0.50 (0.14-1.77)	0.63	0.42
STROKE (n=178)									
HR (95% CI)†	0.81 (0.45-1.47)	0.64 (0.37-1.10)	0.98 (0.59-1.61)	1.00 (Ref)	0.84 (0.49-1.43)	1.01 (0.60-1.71)	0.73 (0.37-1.42)	0.33	0.54

*Log-linear trends across categories of increasing or decreasing GGT, in respect to stable GGT, were tested using the median GGT-change for each category as an ordinal variable in an extended Cox proportional hazards model adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and the period of GGT-change assessment. GGT and triglycerides were log-transformed.

†Estimated from extended Cox proportional hazards models adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and period of GGT-change assessment. GGT and triglycerides were log-transformed.

Supplemental Table 4. All-cause mortality and mortality from cardiovascular disease according to categories of longitudinal GGT-change in males with baseline age ≤60 years and >60 years, VHM&PP 1985-2005

	Longitudinal GGT-change						p for trend GGT decrease*	p for trend GGT increase*	HR per baseline GGT log-unit increase‡	HR per GGT log-unit increase with GGT as time-varying covariate§	
	Decrease			Stable	Increase						
	Pronounced	Moderate	Mild		Mild	Moderate					Pronounced
Age ≤60 years at baseline											
ALL-CAUSE MORTALITY (n=1142), HR (95% CI)†	0.95 (0.74-1.22)	0.96 (0.75-1.22)	0.78 (0.59-1.01)	1.00 (Ref)	1.03 (0.79-1.33)	1.04 (0.80-1.34)	1.48 (1.17-1.87)	0.94	0.001	2.64 (2.18-3.21)	3.29 (2.74-3.95)
TOTAL CVD MORTALITY (n=358), HR (95% CI)†	1.20 (0.75-1.92)	1.11 (0.70-1.77)	0.96 (0.58-1.59)	1.00 (Ref)	1.07 (0.64-1.79)	1.33 (0.83-2.16)	1.72 (1.10-2.69)	0.44	0.009	2.27 (1.61-3.20)	2.68 (1.92-3.73)
CORONARY HEART DISEASE (n=215), HR (95% CI)†	1.20 (0.66-2.19)	1.14 (0.63-2.08)	0.85 (0.44-1.67)	1.00 (Ref)	1.17 (0.61-2.25)	1.43 (0.77-2.64)	1.33 (0.73-2.42)	0.26	0.45	2.63 (1.72-4.04)	2.48 (1.60-3.83)
CONGESTIVE HEART FAILURE (n=23), HR (95% CI)†	0.53 (0.08-3.26)	1.73 (0.44-6.85)	0.59 (0.10-3.56)	1.00 (Ref)	n.a.¶	0.67 (0.11-4.04)	1.26 (0.28-5.73)	0.88	0.55	1.64 (0.37-7.26)	1.76 (0.43-7.17)
STROKE (n=75), HR (95% CI)†	1.31 (0.44-3.91)	0.80 (0.24-2.66)	1.26 (0.40-3.96)	1.00 (Ref)	1.36 (0.41-4.46)	1.62 (0.53-4.97)	2.47 (0.88-6.92)	0.70	0.02	2.50 (1.14-5.47)	3.92 (1.95-7.90)
Age >60 years at baseline											
ALL-CAUSE MORTALITY (n=1162), HR (95% CI)†	0.94 (0.73-1.19)	1.08 (0.86-1.33)	1.00 (0.80-1.24)	1.00 (Ref)	1.08 (0.84-1.35)	1.15 (0.90-1.47)	1.28 (1.01-1.63)	0.74	0.023	1.65 (1.32-2.07)	1.85 (1.41-2.42)
TOTAL CVD MORTALITY (n=628), HR (95% CI)†	0.95 (0.68-1.32)	0.95 (0.71-1.27)	0.91 (0.67-1.23)	1.00 (Ref)	1.07 (0.80-1.48)	1.15 (0.83-1.60)	1.29 (0.93-1.79)	0.57	0.065	1.47 (1.07-2.01)	1.60 (1.10-2.31)
CORONARY HEART DISEASE (n=326), HR (95% CI)†	0.84 (0.53-1.34)	0.86 (0.57-1.30)	0.97 (0.65-1.45)	1.00 (Ref)	1.11 (0.72-1.71)	1.21 (0.80-1.88)	1.08 (0.68-1.72)	0.29	0.43	1.10 (0.71-1.74)	1.52 (0.90-2.55)
CONGESTIVE HEART FAILURE (n=68), HR (95% CI)†	1.15 (0.93-7.20)	0.43 (0.14-1.32)	1.19 (0.48-2.95)	1.00 (Ref)	0.77 (0.27-2.24)	0.96 (0.34-2.84)	1.64 (0.64-4.24)	0.67	0.39	3.59 (1.54-8.42)	2.58 (0.92-7.20)
STROKE (n=153), HR (95% CI)†	1.39 (0.71-2.69)	1.37 (0.76-2.47)	0.75 (0.38-1.45)	1.00 (Ref)	0.94 (0.46-1.93)	1.37 (0.70-2.71)	1.80 (0.94-3.45)	0.29	0.03	1.95 (1.10-3.61)	1.40 (0.68-2.91)

*Log-linear trends across categories of increasing or decreasing GGT, in respect to stable GGT, were tested using the median GGT-change for each category as an ordinal variable in an extended Cox proportional hazards model adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and the period of GGT-change assessment. GGT and triglycerides were log-transformed.

†Estimated from extended Cox proportional hazards models adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and period of GGT-change assessment. GGT and triglycerides were log-transformed.

‡Estimated from Cox proportional hazards models adjusted for baseline age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose. GGT and triglycerides were log-transformed.

§Estimated from extended Cox proportional hazards models adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. GGT and triglycerides were log-transformed.

¶Insufficient events.

Supplemental Table 5. All-cause mortality and mortality from cardiovascular disease according to categories of longitudinal GGT-change in females with baseline age ≤60 years and >60 years, VHM&PP 1985-2005

	Longitudinal GGT-change						p for trend GGT decrease*	p for trend GGT increase*	HR per baseline GGT log-unit increase‡	HR per GGT log-unit increase with GGT as time- varying covariate§	
	Decrease		Stable	Increase							
	Pronounced	Moderate		Mild	Moderate	Pronounced					
Age ≤60 years at baseline											
ALL-CAUSE MORTALITY (n=839), HR (95% CI)†	1.03 (0.77-1.37)	1.16 (0.87-1.53)	0.91 (0.67-1.23)	1.00 (Ref)	1.04 (0.77-1.41)	1.13 (0.84-1.52)	1.41 (1.07-1.84)	0.36	0.005	2.32 (1.82-2.95)	2.75 (2.19-3.45)
TOTAL CVD MORTALITY (n=188), HR (95% CI)†	0.82 (0.45-1.52)	1.29 (0.73-2.26)	0.52 (0.25-1.08)	1.00 (Ref)	1.06 (0.57-1.97)	1.04 (0.56-1.93)	1.30 (0.75-2.25)	0.77	0.35	1.87 (1.12-3.11)	2.47 (1.54-3.95)
CORONARY HEART DISEASE (n=79), HR (95% CI)†	1.20 (0.48-3.04)	1.25 (0.51-3.08)	0.60 (0.20-1.84)	1.00 (Ref)	0.81 (0.28-2.32)	1.24 (0.49-3.14)	1.47 (0.62-3.48)	0.54	0.23	2.12 (0.98-4.61)	1.05 (0.45-2.45)
CONGESTIVE HEART FAILURE (n=14), HR (95% CI)†	n.a.¶	n.a.¶	n.a.¶	1.00 (Ref)	n.a.¶	n.a.¶	n.a.¶	n.a.¶	n.a.¶	n.a.¶	n.a.¶
STROKE (n=57), HR (95% CI)†	0.40 (0.14-1.14)	0.67 (0.26-1.76)	0.41 (0.13-1.33)	1.00 (Ref)	0.82 (0.31-2.15)	0.67 (0.24-1.88)	0.74 (0.30-1.85)	0.16	0.56	2.03 (0.80-5.14)	4.27 (1.96-9.23)
Age >60 years at baseline											
ALL-CAUSE MORTALITY (n=1408), HR (95% CI)†	0.95 (0.76-1.18)	0.94 (0.75-1.16)	0.97 (0.77-1.22)	1.00 (Ref)	1.02 (0.81-1.29)	1.13 (0.90-1.42)	1.14 (0.92-1.41)	0.63	0.17	1.17 (0.95-1.49)	1.39 (1.08-1.79)
TOTAL CVD MORTALITY (n=781), HR (95% CI)†	0.92 (0.69-1.24)	0.89 (0.66-1.19)	0.93 (0.69-1.26)	1.00 (Ref)	1.02 (0.75-1.38)	1.12 (0.83-1.51)	1.10 (0.83-1.47)	0.67	0.52	1.05 (0.78-1.40)	1.21 (0.86-1.70)
CORONARY HEART DISEASE (n=345), HR (95% CI)†	1.13 (0.72-1.77)	1.22 (0.79-1.89)	0.86 (0.52-1.41)	1.00 (Ref)	1.36 (0.85-2.16)	1.29 (0.81-2.06)	1.37 (0.88-2.12)	0.51	0.18	1.25 (0.82-1.89)	1.31 (0.79-2.15)
CONGESTIVE HEART FAILURE (n=83), HR (95% CI)†	0.64 (0.27-1.51)	0.38 (0.13-1.02)	0.98 (0.45-2.15)	1.00 (Ref)	0.68 (0.28-1.66)	0.92 (0.39-2.13)	0.96 (0.43-2.13)	0.27	0.83	0.61 (0.23-1.62)	0.90 (0.30-2.66)
STROKE (n=209), HR (95% CI)†	0.77 (0.44-1.35)	0.71 (0.40-1.24)	1.10 (0.64-1.89)	1.00 (Ref)	0.78 (0.43-1.42)	0.97 (0.55-1.72)	0.94 (0.54-1.61)	0.30	0.85	1.10 (0.63-1.93)	1.41 (0.73-2.72)

*Log-linear trends across categories of increasing or decreasing GGT, in respect to stable GGT, were tested using the median GGT-change for each category as an ordinal variable in an extended Cox proportional hazards model adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and the period of GGT-change assessment. GGT and triglycerides were log-transformed.

†Estimated from extended Cox proportional hazards models adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. All models are additionally adjusted for baseline GGT and period of GGT-change assessment. GGT and triglycerides were log-transformed.

‡Estimated from Cox proportional hazards models adjusted for baseline age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose. GGT and triglycerides were log-transformed.

§Estimated from extended Cox proportional hazards models adjusted for age, body-mass-index, smoking status, occupational status, triglycerides, total cholesterol, systolic and diastolic blood pressure and blood glucose as time-varying covariates. GGT and triglycerides were log-transformed.

¶Insufficient events.