Association Between Speed of Multimorbidity Accumulation in Old Age and Life Experiences: A Cohort Study.

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Funding: The Swedish National study on Aging and Care (SNAC) is supported by the funding from the Swedish Ministry of Health and Social Affairs, the participating county councils and municipalities, and the Swedish Research Council. Financial support from the Swedish Research Council and the Swedish Research Council for Health, Working Life and Welfare is acknowledged. Specific grants were obtained from the Swedish Research Council (2016-00981), the Swedish Research Council for Health, Working Life and Welfare (2017-01764), Karolinska Institutet's Strategic Young Scholar Grants in Epidemiology or Biostatistics (SFO-EPI), Loo and Hans Osterman Foundation (2016-46287, 2017-00242 & 2018-01227), Karolinska Institutet's Foundation Grants for Medical Research, Lindhés Advokatbyrå AB (LA2016-0239 & LA2017-0453), and Stiftelsen Gamla Tjänarinnor (2015-00243).

Conflict of interest: The authors report no conflicts of interest
Running head: Multimorbidity Accumulation and Life Experiences

ABSTRACT

Rapidly accumulating multiple chronic conditions (multimorbidity) during aging are associated with many adverse outcomes. We explored the association between four experiences throughout life – childhood socioeconomic circumstances, early adulthood education, mid-life occupational stress, and late-life social network – and the speed of chronic disease accumulation. We followed 2,589 individuals aged 60+ from the Swedish National Study on Aging and Care in Kungsholmen for nine years (2001/2004 - 2010/2013). Information on life experiences was collected from detailed life history interviews. Speed of disease accumulation was operationalized as the change in the count of chronic conditions obtained from clinical examinations, medical histories, laboratory data, drug-use, and register linkages over nine years. Linear mixed models were used to analyze the data. Speed of disease accumulation was reduced in individuals with more than elementary education (β*time [secondary]: -0.065; 95% CI: -0.126 to -0.004; [university]: -0.118; 95% CI: -0.185 to -0.050), active occupations (β*time [Ref: high-strain jobs]: -0.078; 95% CI: -0.138 to -0.017) and richer social networks (β*time [moderate]: -0.102; 95% CI: -0.149 to -0.055; [rich]: -0.135; 95% CI: -0.182 to -0.088). The association between childhood circumstances and disease accumulation speed was attenuated by later-life experiences. Diverse experiences throughout life may decelerate the speed of chronic disease accumulation during aging.

Keywords: Aging, childhood socioeconomic circumstances, education, life-course, longitudinal, multimorbidity, occupational stress, physical resilience, population-based, social networks.

Abbreviations: ICD, international classification of diseases; SNAC-K, Swedish National Study on Aging and Care – Kungsholmen.

INTRODUCTION

A prevalent view that aging universally manifests as a descent into physical limitation and psychosocial adversity (1) is contradicted by the widespread heterogeneities in the rate of physical, functional, or psychosocial decline observed in late life (2-4). Indeed, a sizeable proportion of the elderly population exhibits more favorable age-related health trajectories than expected (5). One example is multimorbidity, the coexistence of two or more chronic conditions in the same person, which is associated with an array of adverse outcomes in late life, including accelerated functional decline and disability, psychological distress, reduced quality of life, and premature death (6, 7). And while the prevalence of multimorbidity in aging is high, considerable heterogeneities in disease accumulation speed been described (3, 8).

One possibility is that physical resilience, the ability to withstand or recover from functional decline in the face of stressors that disrupt normal physiological homeostasis (9), is depleted in individuals with rapidly accumulating multimorbidity. Physical resilience is constrained by the underlying physiologic reserve which determines the capacity of the system to function beyond its basal level, but is also enhanced by the various environmental and psychosocial inputs (10). Among these inputs, the role of life experiences, such as childhood socioeconomic circumstances, education, work-related stress, and social networks might be especially relevant, given a well-established link between these risk factors and life-long health outcomes (11-14), and their relevance in the biodemographic model of health (15). Several previous studies have examined inter-individual differences in the speed of multimorbidity accumulation, considering, among other things, its association with racial background, obesity, low income, or inflammation (3, 16-22). No study to date has examined the speed of disease accumulation in response to multiple experiences occurring throughout the entire life course.

The aim of this study is to examine the association between experiences occurring across the life course and the speed of chronic disease accumulation in old age. Our hypothesis is that advantageous socioeconomic circumstances in childhood, higher education in early adulthood, reduced occupational stress in midlife, and rich social networks in old age, would be associated with a slower speed of disease accumulation. This study contributes to an emerging field of successful aging by highlighting a set of factors that could help decelerate chronic disease accumulation.

METHODS

Study population

The study population comes from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), an ongoing population-based longitudinal study of adults aged 60+, living at home or in an institution in the Kungsholmen district of Stockholm between 2001 and 2004 (23). A total of 3,363 people were examined at baseline (participation rate 73.3%) and have since undergone regular nurse interviews, physician examinations, cognitive assessments, and laboratory testing. We removed 322 participants with dementia at baseline and 452 individuals with missing information on life experiences, resulting in the analytic sample of 2,589 individuals. They were followed between baseline and three subsequent examinations – the equivalent of nine years of follow-up (see Web Figure 1 for study population flow). SNAC-K was approved by the Regional Ethical Review Board in Stockholm and written informed consent was obtained from participants or their next of kin.

Assessment of chronic diseases

Medical diagnoses were made by the trained physicians based on clinical examination, medical history, laboratory data, and medication use. Linkages to primary care and hospital discharge registers increased the coverage of diagnostic episodes. While self-reports and proxy reports of medical conditions were utilized, they were not sufficient basis for clinical diagnoses in SNAC-K, which required objective verification. The total count of chronic diseases was identified from a comprehensive evaluation of ICD-10 codes by a multidisciplinary team of geriatricians, general practitioners and epidemiologists (24). Chronic diseases were classified as those with prolonged duration and when either (i) residual disability remained or quality of life was worsened, or (ii) a long period of care, treatment or rehabilitation was required. A total of 918 chronic ICD-10 codes were identified and grouped into 60 categories in accordance with clinical criteria and relevance for old age (8, 24). This definition also considers rare diseases and health problems that have a lasting impact on the quality of life of older adults. Chronic conditions deemed as risk factors (e.g. hypertension or dyslipidemia) were excluded from the total count in accordance with previous studies employing similar methodology (7).

Assessment of life experiences

Four experiences occurring over the life course were studied in relation to disease accumulation speed: childhood socioeconomic circumstances, early adulthood education, life-long occupational stress, and old-age social network.

Childhood socioeconomic circumstances

During the baseline nurse interview, study participants reported their fathers' primary occupation around age 16. Professions were classified based on the Swedish socioeconomic classification of

occupations (SEI) representing six occupational groups. Following a previous study using similar protocols (25), we dichotomized father's occupation as manual ([1] unskilled/semiskilled; [2] skilled workers) and non-manual ([3] assistant non-manual; [4] intermediate non-manual; [5] professionals/higher civil servants/executives; [6] self-employed).

Highest-attained level education

Educational attainment was assessed during the baseline interview. The levels of education, and their corresponding mean durations were as follows: unfinished primary education, (approximately 7 years), elementary education (~9.5 years), vocational training (~11 years), gymnasium (~11.6 years), unfinished higher education (~13.8 years), completed university education (~16.1 years), and doctoral education (~20.6 years). For the analysis, a three-level variable was generated: elementary, secondary, and university education.

Occupational stress – longest held job

Occupational information was collected during the baseline interview when participants were inquired about work titles, job tasks, employers, and durations of five longest-held occupations. To assess cumulative occupational stress, we focused on the occupation held the longest during professional life. Only 31 women reported being exclusively engaged in childcare delivery at home and were not considered in the analysis. We used a validated matrix to measure psychosocial conditions at work based on the Karasek model of job demands and decision latitude (26). Job demands refer to the amount of workload as well as time limitations, whereas job control captures decision-making autonomy in conducting work tasks. We dichotomized demand and control scores according to the median. Then, based on the combinations of these variables, we characterized each occupation by job strain: high strain (high job demands and low

job control); active (high demands; high control), passive (low demands; control); and low strain (low demands; high control). This categorization of occupational stress has been used previously in studies of cardiovascular, metabolic, and neurodegenerative diseases (27-29).

Late-life social network

SNAC-K baseline questionnaire included items on social network developed in the National Social Life, Health, and Aging Project (30), encompassing dimensions of size and support. To measure network size, we used information on marital status, living arrangement, number of living children, and the frequency of direct or remote contact with relatives or friends. Network support was assessed by inquiring about satisfaction with various social connections, the extent of perceived material and psychosocial support, and the sense of affinity and belonging to the various groups. All individual indicators were converted into z-scores and averaged separately across size and support components. Since the correlation between the two measures was considerable (0.76), we computed an overall social network index by averaging the two sub-indices of network size and network support. For the analysis, the index of social network (mean= 0.06; SD=0.52) was operationalized according to the tertile distribution: poor network (mean z-score <-0.13), moderate network (-0.13≤ mean z-score≤0.30) and rich network (mean z-score>0.30), which was in accordance with previous studies utilizing categorical measures of the social network (8, 31).

Covariates

In addition to age and sex, we collected information on smoking status (never smoked; ever smoked; current smoker) and alcohol consumption (no/occasional; light-to-moderate; heavy). Baseline data on total number of drugs and underweight (body mass index <18.5) were used to

partially adjust for disease severity, a strategy employed previously in other studies (8, 32). In accordance with a previous study (8), all models were additionally adjusted with a four-level indicator variable: 1) followed-up until the end of the study period [reference category]; 2) died before scheduled follow-up; 3) died after dropping out; 4) alive dropout to partially account for attrition and mortality.

Statistical analysis

Linear mixed models were used to examine the speed of chronic disease accumulation over time. To measure the association between the exposures and the average annual increase in the number of chronic diseases, interactions between follow-up time and life experiences were included as fixed effects. Random effects for individual and follow-up time were included and unstructured covariance structure was assumed. First, each aspect of life experiences was considered individually, followed by mutually-adjusted and fully-adjusted models. To examine exposure combinations, we estimated a set of additional models with parameters indicating the joint presence of life experiences. Formal tests for interaction were carried out in conjunction with the combination analyses. Dropouts (deceased or lost to follow-up) were retained, contributing to the baseline associations, whereas estimating disease trajectories required at least two observations per individual over the follow-up. Additional analysis with quadratic time term (its interaction with life experiences and its inclusion in the random effect) was performed. Finally, we conducted multiple imputation by chained reaction using Rubin's rule. Results presented here are based on the complete case analyses.

RESULTS

Baseline characteristics of the study population are in Table 1. Dropouts were more likely to be older, less educated, and had more baseline chronic conditions, just as those excluded due to missing information on life experiences.

Table 1 here

Associations between life experiences and the speed of disease accumulation over nine years, estimated from four separate mixed linear models are presented in Table 2 (column 2). The parameters of interest are the interactions between each measure and time. Individuals growing up with fathers in non-manual occupations experienced slower disease accumulation speed after age 60 (reference: manual father's occupation), although the result only trended towards statistical significance (p=0.076). Relative to individuals with elementary education, the speed of disease accumulation was reduced in those with secondary and university education in a dose-response manner. Only individuals with active life-long occupations experienced a slower speed of disease accumulation over the follow-up (reference: high strain occupations). Relative to those in the lowest social network tertile, a progressive slow-down in disease accumulation speed was found in those with moderate and large social networks.

Table 2 here

In mutually-adjusted analyses (Web Table 1) and in the fully-adjusted model (Table 2; column 3), the association between childhood socioeconomic circumstances and disease accumulation speed was fully attenuated by later measures of life experiences. Higher education, active life-long occupations, and rich social networks all preserved their association with slower disease

accumulation upon mutual adjustment. Predicted chronic disease trajectories across the levels of life experiences, calculated from the fully-adjusted model, are in Figure 1.

Figure 1 here

We found no evidence of statistically-significant interactions between life experiences. We also explored the joint presence of education, lifelong job stress, and late-life social network for disease accumulation speed (Figure 2). We omitted childhood socioeconomic circumstance from these analyses, since its association was attenuated in mutually-adjusted models. We dichotomized education (low [elementary education] vs. high [secondary and university]), and social network (poor [lowest tertile] vs. rich [tertiles 2 and 3]). We found that active jobs were associated with slower speed of disease accumulation only in the presence of high education (β*time = -0.20, 95% CI: -0.33 to -0.07) (Figure 2; panel A). The combination of low education and poor social network was especially detrimental, since all other scenarios were associated with a decelerated speed of disease accumulation (Figure 2; panel B). Relative to those with high strain jobs and poor social networks, those with poor social networks but in active occupations, experienced slower disease accumulation speed (β*time = -0.15, 95% CI: -0.27 to -0.03), whereas rich social networks were associated with slower disease accumulation speed irrespective of lifelong job stress (Figure 2; panel C).

Figure 2 here

Additional analysis using quadratic time terms revealed very slight acceleration of disease counts towards the end of the follow-up period. The pattern of the association between life experiences

disease accumulation remained unchanged in the analysis with quadratic terms. Results remained unchanged after imputing missing data on life events.

DISCUSSION

In this population-based prospective study, we found slower speed of disease accumulation after age 60 in individuals with higher than elementary education, active life-long occupations, and richer social networks in old age. The association between the speed of chronic disease accumulation and childhood socioeconomic circumstances was attenuated by subsequent life experiences. In the joint analyses, rich social networks emerged as especially noteworthy. Individuals managing to avoid the lowest tertile of late-life social networks experienced slower disease accumulation speed irrespective of life-long job strain. Notwithstanding the importance of old-age social engagement, we also observed that the most desirable combinations of experiences throughout life were associated with the slowest speed of disease accumulation.

Rapidly accumulating multimorbidity likely occurs when progressive cellular and molecular dysfunctions associated with aging can no longer be mitigated by compensatory mechanisms (33, 34). In contrast, individuals capable of maintaining homeostatic capacity due to preserved physical resilience are expected to exhibit slower pace of chronic disease accumulation over time. It has been suggested that physical resilience, the ability to withstand or recover from functional decline after a health stressor (35), could be reflected by the inter-individual differences in longitudinal health trajectories (10). Speed of multimorbidity accumulation could be such a transition, providing a window into physical resilience, especially in light of emerging evidence suggesting that multimorbidity and physical or cognitive decline might share common causal mechanisms involving the basic biological hallmarks of aging (36). Physical resilience is both constrained by the underlying physiologic reserve which determines the capacity of the system to

function beyond its basal level (akin to the concept of intrinsic capacity proposed by the World Health Organization (37)), but is also shaped by the relevant environmental and psychosocial inputs. We examined several aspects of experiences occurring throughout life for their contribution to disease accumulation. Our approach contributes to the emerging literature on physical resilience and successful aging, and is in line with new priorities for multimorbidity research, advocating for capturing its dynamic nature (38) and recognizing diverse contexts and experiences (39, 40).

We found that the association between childhood circumstances and disease accumulation speed was attenuated by subsequent mid- and late-life factors. This is consistent with a previous report in which the association between childhood conditions and multimorbidity was reduced by adult SES and adult health (41). The importance of later-life mediators of childhood circumstances was illustrated in another study (42) in which childhood deprivation interacted with adult income in predicting multimorbidity after age 50, albeit in a cross-sectional setting. The relationship between childhood disadvantage and old-age multimorbidity appears consistent with a pathways model, wherein early life events influence later life experiences, opportunities, and risks, as opposed to the critical period model which emphasizes long-lasting scarring by early deprivation (43).

One possibility is that childhood socioeconomic circumstances help shape educational attainment in early adulthood, which has a much more lasting impact on the speed of disease accumulation. Indeed, our finding of a reduced rate of change in chronic conditions in individuals with higher education is consistent with previous literature (17, 44). Education is a key component of adult socioeconomic position which has been shown to be a major determinant of long-term health (45), with potential pathways involving improved health literacy and health behaviors, enhanced

cognitive reserve, and reduced inflammation. A recent study has found that positive deviations between observed and expected mental well-being, predicted for a given level of physical capability (a proxy of resilience), were associated with higher socioeconomic position (46). This is in line with the recently proposed "life course model of multimorbidity resilience theory" which argues that access to and accumulation of individual, social, and environmental resources helps foster resilience in the face of multimorbidity burden (47).

Few previous studies have considered the association between occupational strain in mid-life and disease accumulation speed in old age. Job strain has been associated with coronary heart disease (48) and cognitive impairment (49), with prolonged exposure durations being especially detrimental. Here we showed that deleterious effects of work stress also extend to the speed of disease accumulation during aging. Several mechanisms linking chronic health outcomes with occupational stress have been proposed, including the dysregulation of the hypothalamus-pituitary-adrenal cortex axis and autonomic nervous system, and deteriorating health behaviors (50). Theory of allostatic load could explain how responses from the systems mobilized to react to stress might become detrimental through repeated activation, chipping away at reserve and resilience (10, 51). A recent study has found that individuals with a history of repeated imbalance between efforts and rewards at work also had a higher estimate of allostatic load index encompassing neuroendocrine, immune, metabolic, cardiovascular, and anthropometric parameters (52). We demonstrated that in addition to the expected negative impact of high strain and passive jobs, low-strain was also associated with disease accumulation. One possibility could be the lack of mental exercise in low-strain occupations, which could lead to the disuse and atrophy of mental abilities, increasing the risk of neurodegenerative conditions in late life (53).

Finally, we reported reduced speed of disease accumulation in individuals with rich social networks. Frequent contact with supportive social connections during old age has been linked with improved physical health, fewer functional limitations, and reduced dementia risk (8, 54-56). The role of integrated social environments has been emphasized in the biopsychosocial model of health and aging, with pathways involving self-efficacy or optimism; behavioral factors; or direct physiological influences on long-term health (57), often through inflammatory pathways (58). It is due to these multifactorial influences that aspects of the social environment are being increasingly recognized as targets for overcoming the challenges associated with the growing burden of multimorbidity (39). Indeed, community-based interventions utilizing the expertise of psychologists, community health workers, or volunteers can be an effective supplement to treatment- oriented approaches of traditional health care systems (59, 60).

This study assessed the joint presence of several life experiences for the speed of disease accumulation. Although statistically significant interactions were absent, we noted important influences of late life social network, negating the deleterious association of occupational strain with disease accumulation. This is consistent with a previous study where social support has been shown to buffer the influences of job demands on psychological well-being (61). Apparent importance of late-life social network could be due to the temporal relationship between entropic stressors and homeostatic mechanisms throughout life (62), with protective factors in close proximity potentially mitigating decompensation at a time when other sources of resilience would have been exhausted. The multifactorial nature of the social network index (encompassing size and support), as well as some reverse causality between baseline health and network self-reports could also contribute to the size of its association with the speed of disease accumulation. Notably, the joint analyses also demonstrated that accumulation of the most desirable

combinations of experiences over the life course was especially beneficial. This hints at the existence of diverse resilience trajectories determined by physiologic reserve capacity with inputs from the accumulation of life course experiences and resources (47).

In addition to multimorbidity, frailty, the predisposition of biologically old persons to experience rapidly worsening health changes, has been identified as another clinical biomarker that could help study the aging process. While the interplay between multimorbidity and frailty likely involves bi-directional and synergetic relationships, especially when it comes to their role in adverse outcomes (63), there are noteworthy differences between the two conditions. Multimorbidity emerges around age 50, whereas frailty only becomes evident much later in life. Multimorbidity does not necessarily convert into frailty, with less than one-fifth of multimorbid individuals also having frailty (64). On the other hand, nearly three-quarters of frail persons also exhibit multimorbidity. This implies that chronic disease burden is an important contributor to the frailty syndrome, and that there are resilience mechanisms mitigating the impact of biologically relevant clinical abnormalities on adverse outcomes.

Limitations of the study include using self-reported measures of life experiences, potentially increasing the misclassification of exposures. Reverse causality between late-life assessments of life experiences and health status cannot be fully rejected. We did not examine potentially relevant influences of stressful life events, such as late-life bereavement. However, we believe these are partly reflected in our estimates for social network, considering that this variable incorporates civil status and social support. The SNAC-K study population is more fit and of higher socioeconomic background, whereas non-participants (27%) had shorter survival, potentially affecting the generalizability. Had we been able to follow these individuals, reported associations would likely be even greater. Attrition due to mortality and dropout may have

affected the results. To try to account for it, we adjusted the analysis with a variable indicating study exit.

In conclusion, we examined the association between life experiences and the change in the number of chronic conditions after age 60 in a prospective population-based cohort study. We found that disease accumulation speed was reduced in individuals with higher early adulthood education, active occupational roles throughout professional life, and larger social networks in old age. The association between childhood socioeconomic circumstances and disease accumulation speed was attenuated by subsequent experiences. Physical resilience is likely depleted in individuals with rapidly accumulating chronic diseases. This resilience, however, might be enhanced by inputs from several life experiences throughout the life course, with long-term accumulation of these inputs being especially important.

ACKNOWLEDGEMENT

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Funding statement: This work was supported by the funders of The Swedish National study on Aging and Care (SNAC): The Ministry of Health and Social Affairs, Sweden; the participating county councils and municipalities; and the Swedish Research Council. Financial support from the Swedish Research Council and the Swedish Research Council for Health, Working Life and Welfare is acknowledged. Specific grants were obtained from the Swedish Research Council (2016-00981), the Swedish Research Council for Health, Working Life and Welfare (2017-01764), Karolinska Institutet's Strategic Young Scholar Grants in Epidemiology or Biostatistics (SFO-EPI), Loo and Hans Osterman Foundation (2016-46287, 2017-00242 & 2018-01227), Karolinska Institutet's Foundation Grants for Medical Research, Lindhés Advokatbyrå AB (LA2016-0239 & LA2017-0453), and Stiftelsen Gamla Tjänarinnor (2015-00243).

Thank yous: The authors would like to express their gratitude to the participants and staff involved in the data collection and management of the SNAC-K study.

Presentation at meetings: European Geriatric Medicine Society (EUGMS) Congress, Berlin, 10-12 October 2018; Geriatric Society of America (GSA) Meeting, Boston, November 14-18 2018.

Conflict of interests. The authors report no conflicts of interest

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Table 1: Baseline characteristics of the study population[a] according to baseline number of chronic conditions in the SNAC-K study (Stockholm, Sweden 2001/2004 – 2010/2013)

Characteristic	0-1 diseases (N=1068)		2 diseases (N=465)		3 diseases (N=388)		4 diseases (N=268)		5+ diseases (N=400)		*p value*[b]
	N	%	N	%	N	%	N	%	N	%	
Age group											<0.001
60-66 years	722	62%	211	18%	116	10%	64	6%	43	4%	
72-78 years	259	33%	155	20%	148	19%	101	13%	128	16%	
81-87 years	77	17%	71	16%	92	21%	69	16%	132	30%	
≥90 years	10	5%	28	14%	32	16%	34	17%	97	48%	
Sex											<0.05
Female	624	39%	290	18%	255	16%	179	11%	257	16%	
Male	444	45%	175	17%	133	14%	89	9%	143	15%	
Body mass index											<0.001
Underweight (<18.5)	8	14%	9	15%	16	28%	9	16%	16	27%	
Normal (18.5-24.9)	495	43%	187	16%	165	14%	114	10%	201	17%	
Overweight (25.0-29.9)	441	43%	197	19%	164	16%	104	10%	124	12%	
Obese (30.0+)	124	37%	72	21%	43	13%	41	12%	59	17%	
Drugs at baseline											<0.001
0-4 drugs	965	56%	336	20%	226	13%	103	6%	79	5%	
≥5 drugs	103	12%	129	15%	162	18%	165	19%	321	36%	
Father's occupation											0.601
Manual occupation	405	40%	184	18%	150	15%	115	11%	163	16%	
Nonmanual occupation	663	42%	281	18%	238	15%	153	10%	237	15%	
Highest attained education											<0.001
Elementary education	105	28%	66	18%	61	16%	60	16%	83	22%	
Secondary education	483	38%	237	19%	190	15%	139	11%	227	18%	
University education	480	51%	162	17%	137	15%	69	7%	90	10%	
Job strain - longest occupation											<0.001
Low strain midlife job	139	33%	63	15%	80	19%	52	13%	86	20%	
Active midlive job	738	45%	295	18%	226	14%	151	9%	225	14%	
Passive midlife job	79	32%	53	21%	37	15%	32	13%	48	19%	
High strain midlfe job	112	39%	54	19%	45	16%	33	12%	41	14%	
Late life social index											<0.001
Poor social network (tertile 1)	225	29%	130	17%	133	18%	102	13%	173	23%	
Moderate social network (tertile 2)	381	43%	172	19%	113	12%	99	11%	131	15%	
Rich social network (tertile 3)	462	50%	163	18%	142	15%	67	7%	96	10%	

[a]For categorization of life experience variables, see Methods section.
[b]Statistical significance calculated using chi-2 test for independence.

Table 2: Associations between life experiences and the speed of chronic disease accumulation in the SNAC-K study over nine years (Stockholm, Sweden 2001/2004 – 2010/2013).

Measures of life experiences[a]	**Life experiences entered into separate models**[b] N=2,589		**All life experiences together**[c] N=2,589	
	β x time[d]	95% CI[e]	β x time	95% CI
Manual father's occupation	0	Referent	0	Referent
Non-manual occupation	-0.034[f]	-0.071, 0.003	0.012	-0.027, 0.051
Elementary education	0	Referent	0	Referent
Secondary education	-0.104[g]	-0.162, -0.047	-0.065[h]	-0.126, -0.004
University education	-0.185[g]	-0.244, -0.125	-0.118[g]	-0.185, -0.050
High strain longest occupation	0	Referent	0	Referent
Active occupation	-0.107[g]	-0.167, -0.047	-0.078[h]	-0.138, -0.017
Passive occupation	0.025	-0.057, 0.108	0.014	-0.097, 0.069
Low strain occupation	-0.008	-0.080, 0.063	-0.016	-0.087, 0.055
Lowest social network tertile	0	Referent	0	Referent

Moderate network tertile	-0.114[g]	-0.161, -0.067	-0.102[g]	-0.149, -0.055
Highest network tertile	-0.164[g]	-0.211, -0.118	-0.135[g]	-0.182, -0.088

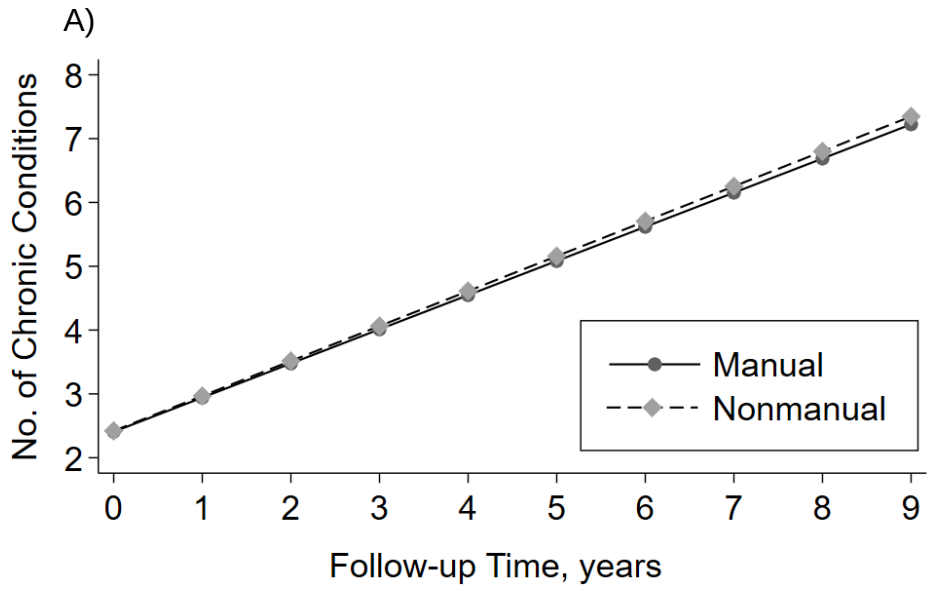
[a]All models adjusted for sex, age, smoking, alcohol, dropout status (dead before follow-up, died after dropping out; alive dropout), underweight, and number of medications at baseline.
[b]Based on four separate mixed linear models.
[c]Based on one fully-adjusted mixed linear model.
[d]Beta coefficients on the interaction between a measure of life experience and time in relation to the accumulation of chronic conditions over nine years of follow-up.
[e]Corresponding 95% confidence intervals
[f]$p<0.1$
[g]$p<0.01$
[h]$p<0.05$

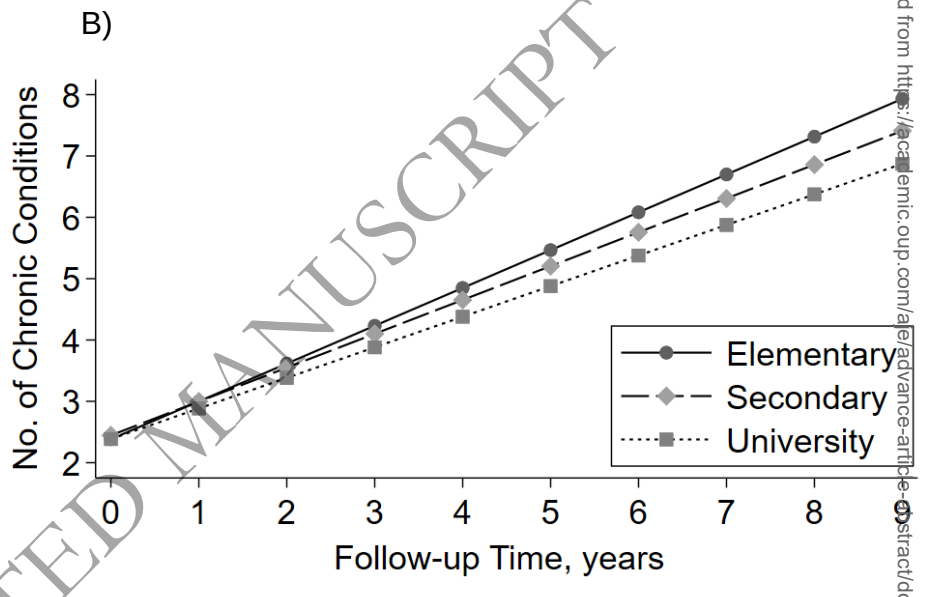
FIGURE LEGENDS

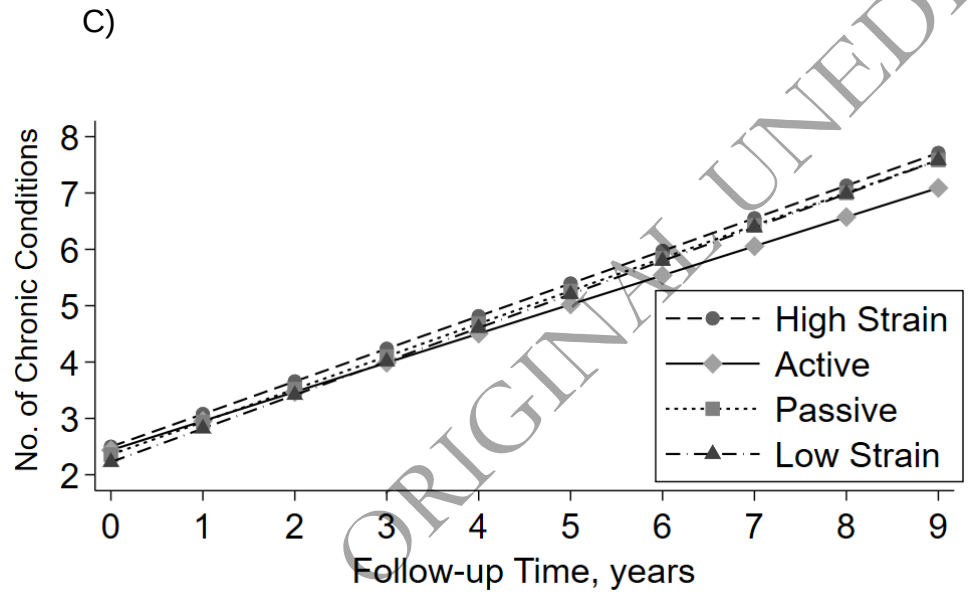
Figure 1: Predicted number of chronic diseases over nine years of follow-up in relation to the four examined life experiences. A) Father's occupation during childhood; B) Early adulthood education; C) Job strain in midlife; D) Social network in late life. Predictions come from one fully-adjusted linear mixed model with all four life experiences included in the estimation. Additional adjustment for sex, age, smoking, alcohol, dropout status (dead before scheduled follow-up, died after dropping out; alive dropout), underweight, number of medications at baseline. For operationalization of life experience factors, see Methods section.

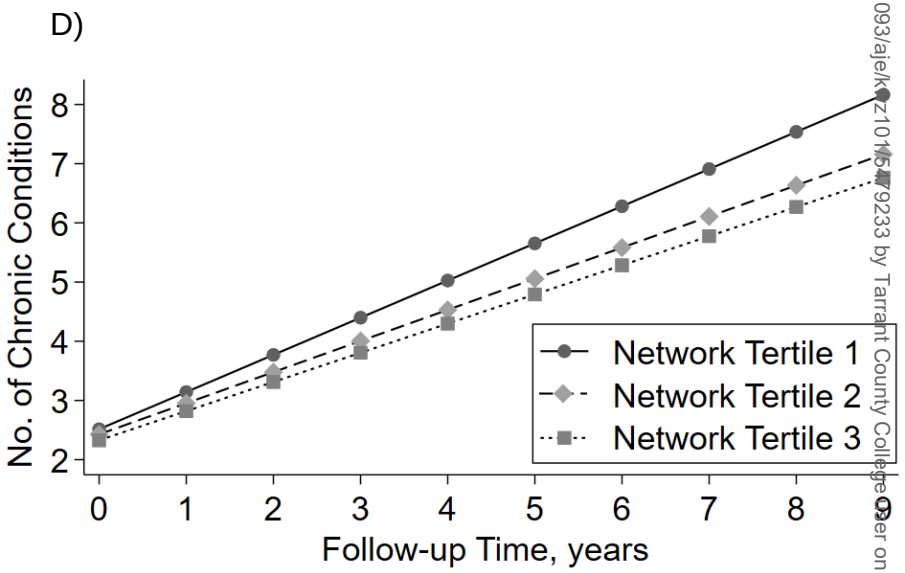
Figure 2: Parameter estimates (beta-coefficients) for the interaction between follow-up time and indicator variables designating combination scenarios of several life experiences: A) Early

adulthood education and midlife job strain; B) Early adulthood education and late life social network; C) Midlife job strain and late life social network. Based on three separate linear mixed models. All models adjused for sex, age, smoking, alcohol, dropout status (dead before scheduled follow-up, died after dropping out; alive dropout), underweight, number of medications at baseline. For operationalization of life experience factors, see Methods section.

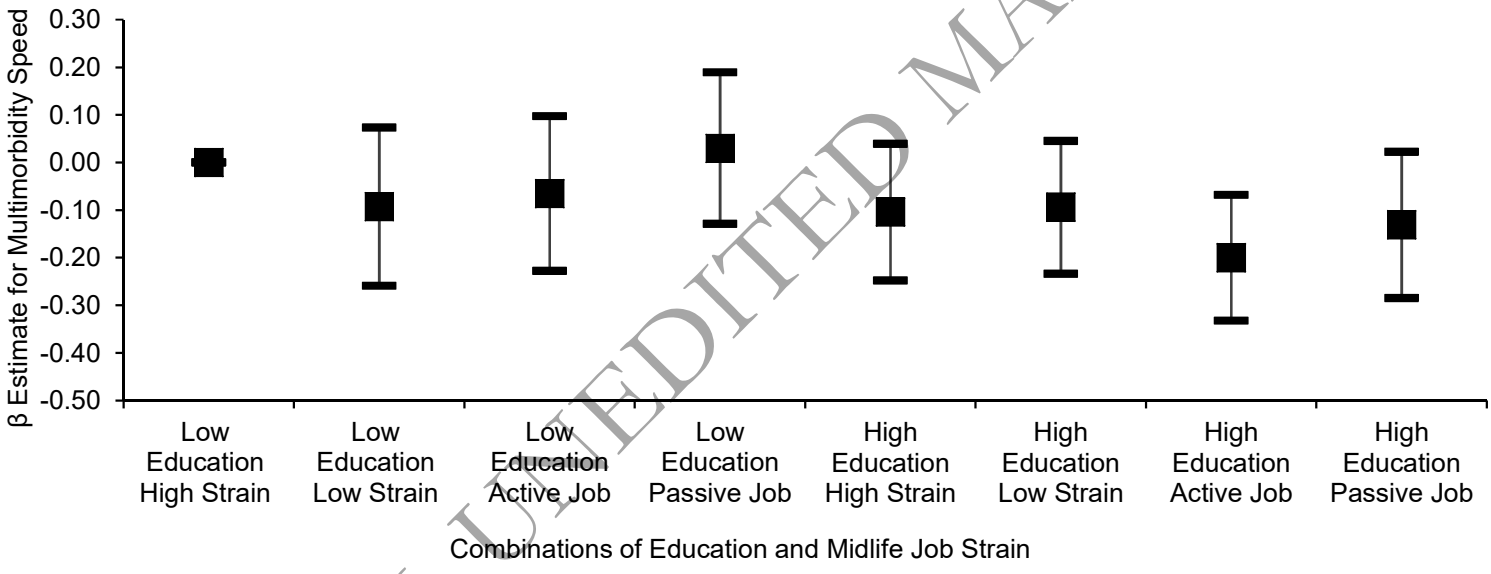




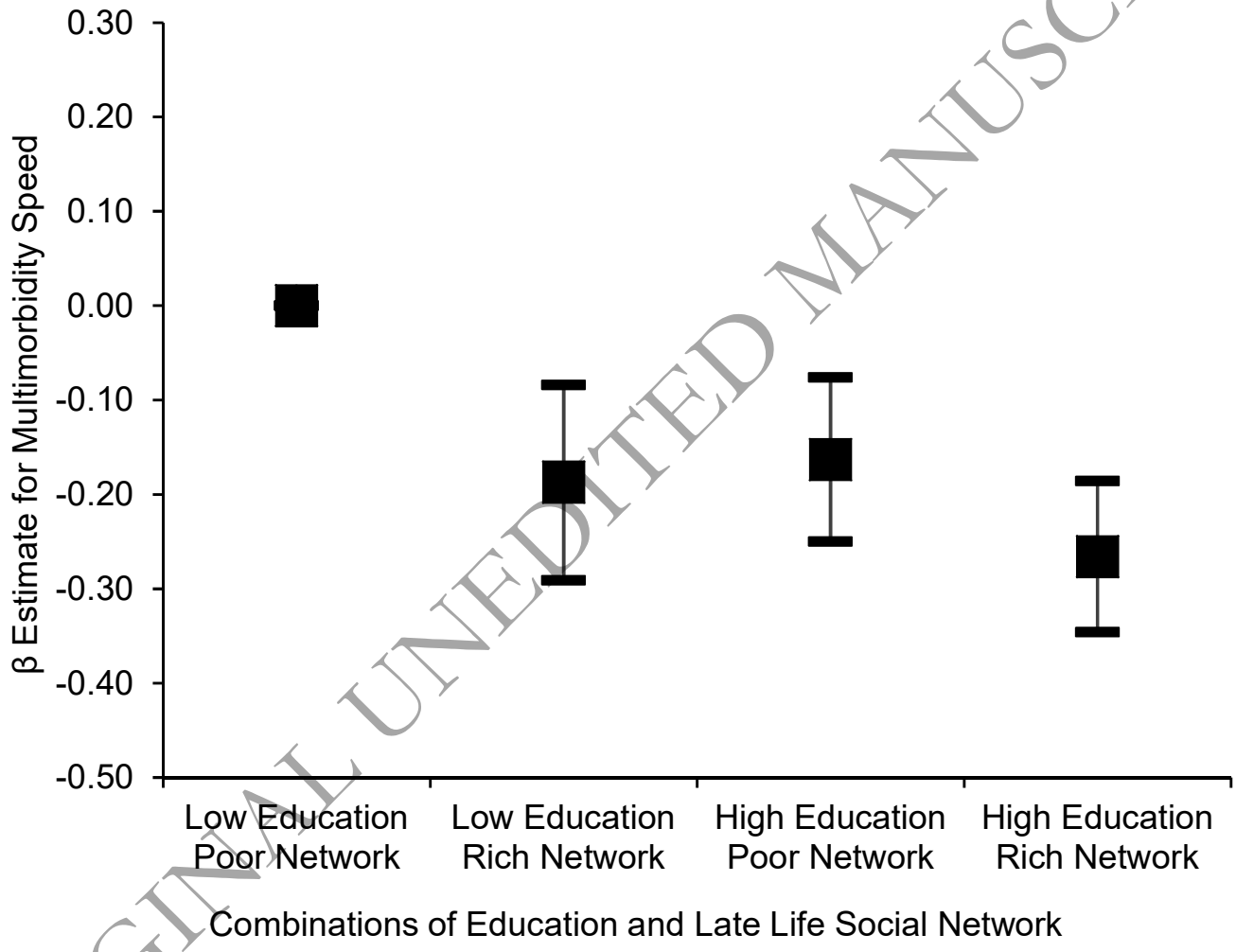




A)



B)



C)