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Authors: Henchoz Y, Seematter-Bagnoud L, Nanchen D, Büla C, von Gunten A, Démonet JF, Santos-Eggimann B

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Childhood adversity: a gateway to multimorbidity in older age?

Yves Henchoz,[a] Laurence Seematter-Bagnoud,[a] David Nanchen,[b] Christophe Büla,[c] Armin von Gunten,[d] Jean-Francois Démonet,[e] Brigitte Santos-Eggimann.[a]

[a] Institute of Social and Preventive Medicine, University of Lausanne Hospital Centre, Lausanne, Switzerland

[b] Department of Ambulatory Care and Community Medicine, University of Lausanne, Switzerland.

[c] Service of Geriatric Medicine and Geriatric Rehabilitation, University of Lausanne Hospital Centre, Lausanne, Switzerland

[d] Service of Geriatric Psychiatry, Department of Psychiatry, University of Lausanne Hospital Centre, Lausanne, Switzerland

[e] Leenaards Memory Centre, University of Lausanne Hospital Centre, Lausanne, Switzerland

Yves.Henchoz@chuv.ch; Laurence.Seematter-Bagnoud@chuv.ch; David.Nanchen@chuv.ch; Christophe.Bula@chuv.ch; Armin.Von-Gunten@chuv.ch; Jean-Francois.Demonet@chuv.ch; Brigitte.Santos-Eggimann@chuv.ch

Corresponding author: Yves Henchoz; Institute of Social and Preventive Medicine (IUMSP), University of Lausanne Hospital Centre, Route de la Corniche 10, CH-1010 Lausanne, Switzerland; yves.henchoz@chuv.ch; Tel.:+41 21 314 88 13

ABSTRACT

Background. Multimorbidity, or co-occurrence of several chronic diseases, has major consequences in terms of function, quality of life and mortality. Recent advances suggest that the aetiology of multimorbidity includes a life-long process. The purpose of this study was to determine the association between childhood adversity and multimorbidity in community-dwelling older adults, and to investigate variation in participants born immediately before, during and at the end of the Second World War.

Methods. Participants were 4731 community-dwelling older adults who enrolled in the Lausanne cohort 65+ study (Switzerland) at age 65-70 years in 2004/2009/2014. A baseline questionnaire provided several indicators of childhood adversity including premature birth, food restrictions, child labour, family economic environment, serious illness/accident, and stressful life events. Multimorbidity at age 67-72 years was defined as ≥2 active chronic diseases at the 2-year follow-up questionnaire.

Results. All childhood adversity indicators except premature birth were significantly associated with multimorbidity. Odds ratio (OR) ranged from 1.23 (P=0.034) for poor family economic environment to 1.74 (P<0.001) for stressful life events. In a multivariable model adjusted for socioeconomic status, health behaviours and stressful life events in adulthood (>16 years), a history of serious illness/accident (OR=1.45; P<0.001) and stressful life events (OR=1.42; P=0.001) in childhood remained significantly associated with multimorbidity. Comparisons between cohorts indicated substantial variations in the prevalence of childhood adversity indicators but similar associations with multimorbidity.

Conclusion. There was an independent association between childhood adversity and multimorbidity after age 65. This study encourages a comprehensive life-course perspective to better understand and potentially prevent multimorbidity.

KEYWORDS

Epidemiology; Multimorbidity; Public health; Life-course

Introduction

Multimorbidity is generally defined as the co-occurrence of two or more chronic diseases or medical conditions. Despite controversies around the operationalization of multimorbidity (Barnett et al., 2012; Calderon-Larranaga et al., 2017), all epidemiological studies converge towards an increasing prevalence with age (Salive, 2013). Half of community-dwelling older adults are affected at age 65 to 74 (Holzer et al., 2017), and more than 80% of those aged 85 years or more (Salive, 2013). Multimorbidity has major consequences on functional independence (Marventano et al., 2014), quality of life (Garin et al., 2014) and mortality (Nunes et al., 2016), and is associated with considerable economic burden (Wang et al., 2017). Whereas a single-disease approach still prevails in many healthcare systems, better understanding and treatment of multimorbidity will only be achieved through a comprehensive, patient-centred approach (Bayliss et al., 2014).

Notwithstanding growing evidence on the public health impact of multimorbidity, and accumulating knowledge on single diseases, the aetiology of multimorbidity remains poorly understood. Whereas investigations were initially oriented towards genetic susceptibility and family history as possible causes (Gijsen et al., 2001), recent studies tend to focus more on socioeconomic (Agborsangaya et al., 2012; Ahmadi et al., 2016; Carvalho et al., 2017; Chung et al., 2015; McLean et al., 2014; Pache et al., 2015; Salive, 2013; Schiotz et al., 2017) and behavioural (Ahmadi et al., 2016; Autenrieth et al., 2013; Cimarras-Otal et al., 2014; Dankel et al., 2017; Dhalwani et al., 2016; Keats et al., 2017; Loprinzi, 2015; Pache et al., 2015; Shi et al., 2015; Wikstrom et al., 2015) risk factors. Overall, these studies indicate that multimorbidity is associated with smoking, alcohol consumption and physical inactivity, and with lower education and income.

Childhood circumstances have also been considered as potential risk factors, based on the assumption that multimorbidity development may be a lifelong process. Childhood adversity refers to a range of potentially difficult or unpleasant situations or experiences, usually before the age of sixteen (Morgan and Gayer-Anderson, 2016). Population-based studies conducted in the US (Pavela and Latham, 2016;

Tucker-Seeley et al., 2011) or Germany (Nagel et al., 2008) indicated that unfavourable childhood socioeconomic conditions are associated with increased number of chronic conditions at older age. Significant associations with multimorbidity in older age were also reported when considering childhood health (Humphreys et al., 2018; Pavela and Latham, 2016) and childhood traumatic events such as abuse (emotional, physical or sexual) or neglect (emotional or physical) (Kamiya et al., 2016; Sinnott et al., 2015; Yen et al., 2013).

Despite valuable studies in this field, a better picture of the long-lasting effects of childhood adversity on multimorbidity at older age is needed. Since none of the previous studies simultaneously covered childhood health, socioeconomic conditions and traumatic events, the relative importance of childhood adversity facets remains unclear. The present study aimed to determine the association between childhood adversity and multimorbidity in community-dwelling older people, using a large set of childhood adversity indicators. Nowadays, the population aged 65 years and over encompasses people born before, during and after the Second World War. A different geopolitical context during childhood has never been taken into account. Therefore, a secondary aim was to compare childhood adversity between three cohorts born before, during and at the end of the Second World War, and to test whether growing up in a different geopolitical context affects the association between childhood adversity and multimorbidity at older age.

Methods

1.1 Study design and population

This study used baseline and 2-year follow-up data from the population-based Lausanne cohort 65+ study (Lc65+). The Lc65+ study enrolment plan has been described previously (Santos-Eggimann et al., 2008). In brief, three representative samples of the general population aged 65 to 70 years and living in Lausanne (the capital of canton of Vaud, Switzerland) were randomly selected in 2004, 2009 and 2014. Participants from these three samples were respectively born before (Pre-war, 1934-1938), during (War, 1939-1943) and at the end (Baby boom, 1944-1948) of the Second World War. Older persons living in an institution or unable to respond by themselves due to advanced dementia were excluded. A baseline questionnaire was sent to randomly selected persons invited to participate (N=3053 in 2004, N=3179 in 2009 and N=3655 in 2014). The number of baseline questionnaires returned was 1564 (51.2%) in 2004, 1489 (46.9%) in 2009 and 1678 (46.0%) in 2014. The present analysis also used data on multimorbidity from the 2-year follow-up mailed questionnaire, which was returned by 1352 participants (86.4%) in 2006, 1285 participants (86.3%) in 2011 and 1418 participants (84.5%) in 2016.

The protocol was approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne (19/04). Written informed consent was obtained from the participants.

1.2 Measures

Information about childhood adversity and covariates was collected through the Lc65+ baseline questionnaire (2004/2009/2014), whereas multimorbidity was assessed through the 2-year follow-up questionnaire in 2006/2011/2016.

1.2.1 Childhood adversity

Participants answered questions about *premature birth* (“Have you ever been told that you were born prematurely?”), *food restrictions* (“Did you suffer from food restrictions before the age of 16 years?”), *child labour* (“Did you have to work in childhood more than twice weekly (e.g. work in the fields, deliveries, etc.)?”), *family economic environment* (“In what family economic environment did you live most of your years between your birth and the age of 10 ? ‘difficult or very difficult’; ‘medium, rather difficult’; ‘medium, rather affluent’; ‘affluent or very affluent’”), and *serious illness or accident* (“Did you have any illness or accident between your birth and the age of 16 threatening your life or preventing you from living like other children?”). In addition, participants were asked whether they experienced any of the following *stressful life events* between their birth and the age of 16 years: death of a family member or another person whom they lived with, parents’ divorce or separation, remoteness of father or mother for longer than 6 months, residing in a boarding house without their family, serious illness or accident of a family member, parental alcoholism or drug abuse, parental unemployment or business failure, physical or emotional aggression (including abuse and neglect), change of country or linguistic region, other events.

1.2.2 Multimorbidity

Participants were asked whether they did suffer from symptoms or received treatment during the previous 12 months for any of 13 common health conditions diagnosed by a physician: hypertension, coronary heart disease, other heart diseases, stroke, diabetes mellitus, chronic respiratory disease, asthma, osteoporosis, arthritis, cancer, gastrointestinal ulcer, depression and Parkinson’s disease. The number of medical conditions was categorized as 0, 1 or ≥2 and multimorbidity was defined as the co-occurrence of two or more medical conditions.

1.2.3 Covariates

Covariates were chosen a priori based on previous studies reporting them to be associated with multimorbidity. *Problematic alcohol consumption* was addressed by asking participants if they experienced problems with excessive alcohol drinking at any point in their lives. *Smoking* status was assessed as 'current smoker', 'former smoker' or 'never smoker'. *Body Mass Index (BMI)* was calculated from self-reported height and weight. *Physical activity* was self-reported and was defined as low if all three following criteria were met: 1) <20 min of sport activity once a week; 2) <30 min of walking three times a week; and 3) avoidance of climbing stairs or carrying light loads in daily activities [2]. The highest level of *education* achieved was assessed as 'basic compulsory' [International Standard Classification of Education [ISCED] (UNESCO, 2011) level 0-2]; 'apprenticeship' [ISCED level 3]; 'post-compulsory' [ISCED level 4-8]. Country of birth was categorized as Switzerland or other countries. Participants also indicated their *living arrangement* ('alone'; 'with others'), and whether they currently received means-tested *supplemental retirement benefits*. Participants were asked whether they experienced any of the following *stressful life events in adulthood* (≥17 years old): divorce or separation, separation of one's minor child for more than 6 months, illness or accident of one's child (without death), death of one's child, illness or accident of the spouse (without death), death of the spouse, illness or accident of another close relative (without death), death of another close relative, physical aggression, unemployment or business failure, unplanned pregnancy (women only), other.

1.3 Statistical analysis

Pearson Chi-squared tests were used to test baseline characteristics differences according to multimorbidity status, as well as differences between the three cohorts in terms of childhood adversity. A Kruskal-Wallis test was performed to determine if age distribution differed significantly according to multimorbidity status. Bivariable associations between study variables were assessed using linear regression. Beta coefficients were adjusted for cohort and sex. The prevalence of multimorbidity was calculated with 95% confidence interval according to the presence or absence of each childhood adversity

indicator. Logistic regression models were calculated to determine the indicators of childhood adversity associated with multimorbidity. First, separate models were built for each childhood adversity indicators. Then a single model included all childhood adversity indicators to estimate their mutually adjusted association with multimorbidity. Multicollinearity between the explanatory variables was assessed using the variance inflation factor, which should not be over 2.5, and by examining the coefficient estimates' precision, which should not be notably lower in the mutually adjusted models compared to the separate models. Models were adjusted for sex and cohort (model 1), and additionally for education, stressful life events in adulthood, problematic alcohol consumption, smoking, supplemental retirement benefits and living arrangement (model 2). All two-order interactions between sex, cohort and indicators of childhood adversity were tested. Model fit was assessed using Likelihood ratio χ^2, Akaike information criterion (AIC) and Bayesian information criterion (BIC). Multinomial logistic regression was used to explore the associations between childhood adversity and multimorbidity when the latter is defined according to an increasing number of comorbidities (0 vs 1, 2, 3 or $\geq$4).

Two sensitivity analyses were carried out. Since depression was likely to influence participants' answers to childhood adversity and hence to inflate the association between childhood adversity and multimorbidity, a first sensitivity analysis was performed by computing multimorbidity without depression and by including depression in adjustment variables in the fully adjusted models (model 2). A second sensitivity analysis was conducted to adjust for potential attrition bias. Associations between childhood adversity and multimorbidity were adjusted for attrition bias using either sampling weights (sensitivity analysis 2A) to keep participants at 2-year representative of the baseline sample, or multiple imputations (sensitivity analysis 2B) to impute missing data and perform analyses on imputed data. Fifty imputation datasets were created with chained equations, assuming that data were missing at random (White et al., 2011). Analyses were conducted using Stata 15.0 software (StataCorp, College Station, TX). Significance was set at $P<0.05$.

Results

Baseline characteristics of participants according to multimorbidity status are displayed in **Table 1**. Overall, 1103 (27.4%) reported multimorbidity. Compared to participants with zero or one medical condition, multimorbid participants were older (P=0.020), reported lower educational level (P=0.007), and were more likely to live alone (P<0.001) and to receive supplemental retirement benefits (P<0.001). As indicated in **Supplementary Table S1**, the prevalence of each single medical conditions did not change significantly across cohorts, except gastrointestinal ulcer that significantly decreased (P=0.009) in women from the Pre-war to the War cohorts. The proportion of participants with zero, one or multiple medical conditions did not change significantly across Pre-war, War and Baby boom cohorts.

As detailed in **Table 2**, there were substantial differences between cohorts in childhood adversity. Irrespective of country of birth, a sharp decrease across cohorts was observed in both women and men regarding the prevalence of food restrictions (all P<0.001) and child labour (all P≤0.006). The proportion of participants reporting a poor family economic environment (from birth to age 10) also decreased across cohorts in men born in Switzerland (P=0.013) or other countries (P=0.005). Specifically in participants born in Switzerland, a significant difference between cohorts was noted in serious illness or accident (men only; P=0.004), whereas in participants born in other countries, significant differences between cohorts were observed in premature birth (men only; P=0.009) and stressful life events (women only; P=0.005).

Bivariable associations between childhood adversity indicators, education, stressful life events in adulthood, problematic alcohol consumption, smoking, low physical activity, BMI and the number of comorbidities, adjusted for cohort and sex, are indicated in **Supplementary Table S2**. The number of comorbidities was weakly but significantly associated with all study variables except premature birth. In contrast, premature birth was significantly associated with stressful life events in childhood (β=0.06; P=0.001), but with none of the other study variables.

Table 3 presents the prevalence (95% confidence interval) of multimorbidity in the presence or absence of each childhood adversity indicators, as well as associations between childhood adversity indicators and multimorbidity. When childhood adversity indicators were analysed in separate models, odds ratios for multimorbidity adjusted for sex and cohort (model 1) were significant for all indicators except premature birth. In the fully adjusted models (model 2), food restrictions (odds ratio (OR) =1.23; P=0.039), serious illness or accident (OR=1.52; P<0.001), and reporting two or more stressful life events (OR=1.55; P<0.001) were significantly associated with multimorbidity. In mutually adjusted models, odds ratios for multimorbidity adjusted for sex and cohort (model 1) were significant for child labour (OR=1.22; P=0.025), serious illness or accident (OR=1.53; P<0.001), and with reporting two or more stressful life events (OR=1.54; P<0.001). In the fully adjusted model (model 2), only serious illness or accident (OR=1.45; P<0.001), and reporting two or more stressful life events (OR=1.42; P=0.001) remained significantly associated with multimorbidity.

Multinomial logistic regression indicated increasing odds of 2, 3 and 4+ medical conditions compared to 0 medical condition (reference category) when the independent variable was either serious illness or accident (**Figure 1A**) or ≥2 stressful life events (**Figure 1B**). None of the interactions between sex and cohort, between sex and indicators of childhood adversity, as well as between cohort and indicators of childhood adversity, was significant. This argues against a differential association between childhood adversity and multimorbidity according to sex or cohort. Similarly, the number of comorbidities in each category of childhood adversity indicators showed a comparable pattern within each of the three cohorts when they were examined separately (**Supplementary Table S3**).

In the first sensitivity analysis, the associations between childhood adversity indicators and multimorbidity calculated without depression persisted, even after additional adjustment for depression in model 2 (**Supplementary Table S4**). The second sensitivity analysis using either sampling weights (**Supplementary Table S5**) or multiple imputations (**Supplementary Table S6**) also confirmed the conclusions drawn from the main analysis.

Discussion

This study investigated the association between childhood adversity and multimorbidity in a large representative sample of community-dwelling older people. A unique contribution of this work is to provide detailed information on multiple aspects of childhood adversity. In particular, multimorbidity in older age was independently associated with a history of serious illness or accident or stressful life events in childhood, whereas associations with food restrictions, child labour and poor family economic environment in childhood did not persist when all adversity indicators were mutually adjusted.

The overall prevalence of multimorbidity of 27.4% is within the 13% to 72% range of values previously reported at age seventy-five (Fortin et al., 2012), yet somewhat lower than the average prevalence of 51% reported at age 65 to 74 in a recent systematic review (Holzer et al., 2017). Several factors may explain this difference. First, the age range in the present study (65 to 70 years) covers only the first half of the age range 65 to 74 years, and it is well accepted that multimorbidity increases with age (Salive, 2013). Then, the prevalence of multimorbidity is lower in the general population (as in the present study) than in clinical settings, or when the period considered is the last 12 months (as in the present study) compared to lifetime (Holzer et al., 2017). Finally, the criteria defining the presence of each medical conditions in the present study (diagnosed by a physician and requiring treatment or causing pain or symptoms) may be more rigorous than in previous studies. On the contrary, data source (e.g. self-reports, administrative data) does not seem to have a relevant effect (Holzer et al., 2017). The sex-specific prevalence of multimorbidity observed in the present study is consistent with previous estimates that reported only moderate differences between women and men at age sixty-five to seventy-four (Agur et al., 2016; Holzer et al., 2017).

Several mechanisms have been proposed to explain how childhood adversity can affect health later in life. At the behavioural level, previous research indicated an association between childhood adversity and adoption of unhealthy lifestyle behaviours as a means of coping with stress, and negative consequences in adulthood in terms of increased morbidity and mortality (Boyce, 2014). However, in this study the link

between childhood adversity and multimorbidity largely persisted after adjustment for smoking, problematic alcohol consumption, physical activity and BMI. Previous work conducted in older people also reported independent associations between multimorbidity and childhood health (Humphreys et al., 2018; Pavela and Latham, 2016) or adverse childhood experiences (Sinnott et al., 2015). Since studies supporting a mediating role of behavioural factors focused on single diseases rather than on multimorbidity, and were essentially conducted in young adults, a plausible explanation could be that behavioural factors play a less important role in the aetiology of multimorbidity compared to single chronic diseases. An alternative hypothesis is that mediation by unhealthy lifestyle behaviours may become less apparent in older age because of early deaths. At the biological level, human and animal research showed that childhood adversity triggers molecular mechanisms implicating physiological disruption that predisposes individuals to diseases across the life span (Berens et al., 2017). At the multisystem level, childhood adversity may favour multimorbidity by accelerating aging. A recent meta-analysis indicated a link between childhood adversity and accelerated telomere shortening, a marker of cellular aging (Ridout et al., 2018). In turn, a longitudinal association was observed between accelerated development of aging phenotypes such as body composition, energetics, inflammation and neurodegeneration, and accumulation of chronic diseases (Fabbri et al., 2015).

The association between childhood adversity and multimorbidity was independent of cohort membership (i.e. participants born before, during or at the end of the Second World War). This may seem contradictory with the differences in childhood adversity indicators observed between cohorts. However, the strongest differences in childhood adversity between cohorts were observed in the prevalence of food restrictions and child labour, whose association with multimorbidity was not significant in the fully adjusted model, whereas differences between cohorts were small or even not significant for stressful life events and serious illness or accident, respectively, whose association with multimorbidity persisted in the fully adjusted model.

Several potential limitations should be considered. First, the observational nature of this study precludes definitive causal inference. Nevertheless, the assessment of multimorbidity at 2-year follow-up limits the possibility for reverse causality, i.e. exaggerated self-rated childhood adversity because of multimorbidity. Second, childhood adversity indicators may have been subject to recall bias. To limit this possibility, the Lc65+ enrolment questionnaire was organized in chronological sections from childhood to current health status in order to enhance recall (Santos-Eggimann et al., 2008). In addition, a mood-congruent memory bias (i.e. selective recall of childhood memories congruent with one's current mood) cannot be excluded. However, if present this bias likely had only a very limited influence on the main conclusions, as suggested by the essentially unchanged results of the sensitivity analysis that adjusted for current depression. Third, as the study sample is representative of community-dwelling older people, individuals who suffered the most severe consequences of adversity in childhood may have been institutionalized or already deceased. However, this potential survival bias may actually have attenuated the associations presently observed. Finally, the geopolitical context in Switzerland, a neutral country during the Second World War, may have implications for external validity of the findings. Country of birth was however taken into account in the fully adjusted models. Furthermore, while Switzerland was little affected by military conflicts during WWII, its location surrounded by belligerents did not spare the civil population from food restrictions and economic consequences of the war, despite a strategical plan of self-sufficiency in food called “Plan Wahlen” that did not deem totally successful (Schwarz, 1980).

In conclusion, this population-based study of community-dwelling older adults found significant associations between several indicators of childhood adversity and multimorbidity. Particularly, serious illness or accident and stressful life events in childhood were both independently associated with multimorbidity at older age. These findings call for a comprehensive life-course perspective of efforts directed at improving the understanding and management of multimorbidity. For children of today and tomorrow, the prevention of childhood adversity should improve. For those of yesterday, researchers and clinicians should focus more on the roots in childhood of adult diseases.

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Declarations of interest

None.

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Table 1. Demographic and socioeconomic characteristics of community-dwelling older women and men according to multimorbidity status

	Total	Number of medical conditions			P
		0 (N=1500)	1 (N=1416)	≥2 (N=1103)	
Sex (N=4,055)					
Women	2353 (58.0%)	836 (55.7%)	835 (59.0%)	660 (59.8%)	0.073 [a]
Men	1702 (42.0%)	664 (44.3%)	581 (41.0%)	443 (40.2%)	
Age (N=4,055)					
Median (IQR)	67.8 (2.5)	67.7 (2.6)	67.8 (2.4)	68.0 (2.6)	0.020 [b]
Mean (SD)	67.9 (1.5)	67.8 (1.5)	67.8 (1.4)	68.0 (1.5)	
Education (N=3,989)					
Basic compulsory	747 (18.7%)	258 (17.4%)	249 (17.9%)	230 (21.2%)	0.007 [a]
Apprenticeship	1562 (39.2%)	555 (37.5%)	559 (40.2%)	437 (40.4%)	
Post compulsory	1680 (42.1%)	668 (45.1%)	582 (41.9%)	416 (38.4%)	
Country of birth (N=4,050)					
Switzerland	2935 (72.5%)	1099 (73.3%)	1027 (72.7%)	784 (71.1%)	0.463 [a]
Other	1115 (27.5%)	400 (26.7%)	386 (27.3%)	318 (28.9%)	
Living arrangement (N=4,046)					
Alone	1535 (37.9%)	523 (34.9%)	519 (36.8%)	482 (43.8%)	<0.001 [a]
With others	2511 (62.1%)	975 (65.1%)	892 (63.2%)	619 (56.2%)	
Suppl. retirement benefits (N=3,995)					
No	3543 (88.7%)	1345 (91.2%)	1256 (90%)	912 (83.8%)	<0.001 [a]
Yes	452 (11.3%)	130 (8.8%)	140 (10%)	176 (16.2%)	

Data are Number (Percent) except age

[a] Pearson Chi-squared test

[b] Kruskal-Wallis test

IQR=interquartile range; SD=standard deviation

Table 2. Childhood adversity among community-dwelling older women and men from three successive cohorts, according to country of birth

	Women (N=2,353)				Men (N=1,702)			
	Pre-war (N=800)	**War (N=758)**	**Baby boom (N=795)**	**P [a]**	**Pre-war (N=552)**	**War (N=527)**	**Baby boom (N=623)**	**P [a]**
Country of birth: Switzerland								
Premature birth (N=2,828)	5.6%	5.6%	4.3%	0.527	4.2%	3.7%	4.5%	0.853
Food restrictions (N=2,918)	22.8%	12.8%	6.7%	<0.001	30.0%	14.1%	6.1%	<0.001
Child labour (N=2,914)	26.6%	17.2%	14.7%	<0.001	35.1%	30.4%	21.1%	<0.001
Poor family economic environment (N=2,920)	13.6%	12.6%	10.1%	0.171	17.9%	16.8%	11.1%	0.013
Serious illness or accident [b] (N=2,885)	13.9%	16.5%	15.9%	0.454	16.4%	23.7%	14.9%	0.004
Stressful life events (N=2,853)								
0	37.4%	44.0%	45.0%	0.066	41.5%	46.9%	49.0%	0.122
1	35.7%	30.1%	31.2%		32.0%	29.3%	31.4%	
≥2	26.9%	26.0%	23.8%		26.6%	23.9%	19.7%	
Country of birth: Other								
Premature birth (N=1,063)	3.6%	6.3%	4.1%	0.419	2.0%	2.5%	8.2%	0.009
Food restrictions (N=1,096)	55.2%	34.9%	21.2%	<0.001	54.3%	36.8%	24.7%	<0.001
Child labour (N=1,110)	27.0%	14.3%	19.4%	0.006	48.4%	28.0%	27.1%	<0.001
Poor family economic environment (N=1,111)	19.3%	17.3%	19.3%	0.831	32.3%	23.2%	17.0%	0.005
Serious illness or accident [b] (N=1,089)	19.7%	14.6%	18.1%	0.397	15.3%	14.0%	21.0%	0.185
Stressful life events (N=1,078)								
0	16.7%	29.7%	32.2%	0.005	22.9%	33.3%	28.7%	0.242
1	33.8%	27.2%	28.7%		29.4%	27.0%	32.2%	
≥2	49.5%	43.1%	39.1%		47.7%	39.6%	39.2%	

[a] Pearson Chi-squared test

[b] Birth defects, problems related to prematurity, serious accident, cancer, tuberculosis, poliomyelitis, other

Table 3. Associations between childhood adversity and multimorbidity in older age

	N	Prevalence of multimorbidity	Separate models [a]		Mutually adjusted models [b]	
			Model 1 [c]	Model 2 [d]	Model 1 [c] (N=3,646)	Model 2 [d] (N=3,311)
Premature birth		% (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
No	3,679	27.3% (25.8-28.7)	Ref.	Ref.	Ref.	Ref.
Yes	181	29.8% (23.3-37.1)	1.13 (0.81-1.57)	1.07 (0.75-1.53)	1.07 (0.76-1.50)	1.02 (0.71-1.48)
Food restrictions						
No	3,140	26.3% (24.7-27.9)	Ref.	Ref.	Ref.	Ref.
Yes	842	31.8% (28.7-35.1)	1.32 ** (1.11-1.56)	1.23 * (1.01-1.50)	1.14 (0.94-1.39)	1.13 (0.91-1.40)
Child labour						
No	3,030	26.3% (24.8-27.9)	Ref.	Ref.	Ref.	Ref.
Yes	962	31.0% (28.1-34.0)	1.27 ** (1.08-1.50)	1.11 (0.92-1.35)	1.22 * (1.03-1.46)	1.06 (0.86-1.30)
Poor family economic environment						
No	3,382	26.8% (25.3-28.3)	Ref.	Ref.	Ref.	Ref.
Yes	618	30.9% (27.3-34.7)	1.23 * (1.02-1.48)	1.08 (0.87-1.33)	0.98 (0.79-1.22)	0.94 (0.74-1.19)
Serious illness or accident						
No	3,285	25.7% (24.2-27.2)	Ref.	Ref.	Ref.	Ref.
Yes	658	35.7% (32.0-39.5)	1.62 *** (1.35-1.93)	1.52 *** (1.25-1.84)	1.53 *** (1.27-1.85)	1.45 *** (1.18-1.79)
Stressful life events						
0	1,521	23.1% (21.0-25.3)	Ref.	Ref.	Ref.	Ref.
1	1,221	26.5% (24.0-29.0)	1.20 * (1.00-1.42)	1.17 (0.97-1.42)	1.13 (0.94-1.36)	1.13 (0.93-1.38)
≥2	1,158	34.5% (31.7-37.3)	1.74 *** (1.47-2.07)	1.55 *** (1.28-1.88)	1.54 *** (1.28-1.85)	1.42 ** (1.15-1.74)
Model fit						
Likelihood ratio χ^2					67.8	227.3
P					<0.001	<0.001
AIC					4234	3691
BIC					4302	3844

[a] childhood adversity indicators in separate models; [b] childhood adversity indicators mutually adjusted

[c] adjusted for sex and cohort; [d] adjusted for sex, cohort and covariates (socioeconomic status, behaviours and stressful life events in adulthood)

OR=odds ratio; CI=confidence interval; AIC=Akaike information criterion; BIC=Bayesian information criterion; * P<0.05; ** P<0.01; *** P<0.001

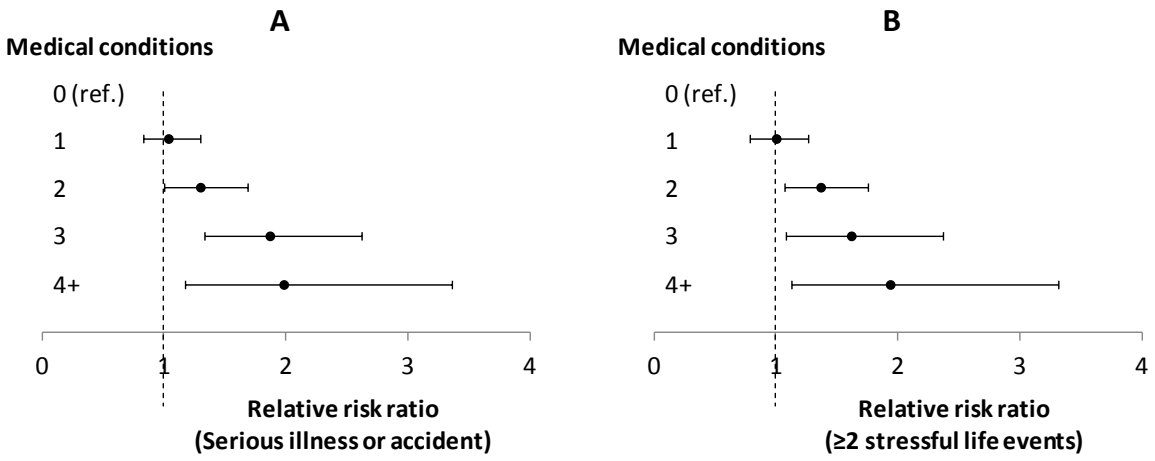

Figure 1. Multinomial logistic regression predicting morbidity (reference: no chronic condition) by serious illness or accident (A) and ≥2 stressful life events (B) in childhood, adjusting for sex, cohort, education, country of birth, stressful life events in adulthood, problematic alcohol consumption, smoking, supplemental retirement benefits and living arrangement (model 2).

Supplementary Table S1. Prevalence of 13 medical conditions among community-dwelling older women and men from three successive cohorts

	Women (N=2,331)				Men (N=1,688)			
	Pre-war (N=790)	War (N=752)	Baby boom (N=789)	P [a]	Pre-war (N=549)	War (N=523)	Baby boom (N=616)	P [a]
Hypertension	32.0%	29.4%	28.0%	0.208	32.2%	34.6%	37.0%	0.232
Coronary heart disease	2.8%	1.9%	2.7%	0.447	6.0%	5.4%	4.9%	0.690
Other heart diseases	3.5%	3.2%	4.4%	0.411	5.1%	6.1%	5.4%	0.749
Stroke	1.1%	0.7%	0.8%	0.562	1.1%	1.0%	1.3%	0.858
Diabetes mellitus	5.9%	6.6%	6.3%	0.852	13.1%	15.5%	12.5%	0.313
Chronic respiratory disease	5.2%	4.0%	5.3%	0.409	4.7%	5.0%	5.0%	0.971
Asthma	4.6%	5.1%	6.1%	0.381	3.6%	2.9%	3.6%	0.739
Osteoporosis	13.2%	11.8%	11.2%	0.459	0.7%	1.7%	1.3%	0.338
Arthritis	29.5%	32.7%	29.0%	0.233	16.8%	16.1%	14.3%	0.485
Cancer	4.2%	3.1%	3.5%	0.497	4.4%	6.9%	7.3%	0.088
Gastrointestinal ulcer	2.5%	0.7%	1.3%	0.009	1.6%	1.5%	1.1%	0.746
Depression	5.4%	5.6%	5.1%	0.897	4.0%	4.0%	3.7%	0.961
Parkinson's disease	1.0%	0.3%	1.0%	0.156	1.5%	0.4%	0.6%	0.126
Number of medical conditions								
0	33.9%	35.2%	38.4%	0.319	40.8%	38.6%	38.6%	0.579
1	36.1%	37.4%	34.1%		33.9%	32.9%	36.2%	
≥2 (multimorbidity)	30.0%	27.4%	27.5%		25.3%	28.5%	25.2%	

[a] Pearson Chi-squared test

Supplementary Table S2. Bivariable associations between study variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Premature birth	–												
2. Food restrictions	0.00	–											
3. Child labour	-0.01	0.16***	–										
4. Poor family economic environment	0.02	0.34***	0.22***	–									
5. Serious illness or accident	0.03	0.11***	0.02	0.06***	–								
6. Stressful life events (childhood)	0.06**	0.23***	0.13***	0.25***	0.14***	–							
7. Education	0.01	-0.08***	-0.35***	-0.14***	0.01	-0.04*	–						
8. Stressful life events (adulthood)	0.02	0.10***	0.02	0.08***	0.09***	0.23***	0.02	–					
9. Problematic alcohol consumption (lifetime)	0.00	0.02	0.06***	0.02	0.02	0.06***	-0.04**	0.09***	–				
10. Smoking	-0.02	-0.01	0.00	-0.02	0.01	0.02	0.01	0.09***	0.11***	–			
11. Low physical activity	-0.01	0.03*	0.02	0.01	0.05**	0.02	-0.05**	0.06***	0.09***	0.05**	–		
12. Body Mass Index	0.02	0.04*	0.13***	0.05**	0.03*	0.06**	-0.17***	0.01	0.02	-0.05**	0.10***	–	
13. Number of comorbidities	0.01	0.08***	0.06***	0.07***	0.09***	0.12***	-0.06***	0.09***	0.04**	0.05**	0.11***	0.20***	–

Standardized beta coefficients adjusted for cohort and sex

* P<0.05; ** P<0.01; *** P<0.001

Supplementary Table S3. Number of comorbidities by childhood adversity indicators in Pre-war, War and Baby boom cohorts

	Pre-war		War		Baby boom	
	N	**Number of comorbidities**	**N**	**Number of comorbidities**	**N**	**Number of comorbidities**
		Mean (95%CI)		**Mean (95%CI)**		**Mean (95%CI)**
Premature birth						
No	1,228	1.04 (0.98-1.10)	1,182	1.03 (0.97-1.09)	1,269	1.00 (0.94-1.06)
Yes	58	1.02 (0.74-1.30)	57	1.05 (0.80-1.31)	66	1.21 (0.92-1.51)
Food restrictions						
No	885	0.98 (0.91-1.05)	1,015	0.99 (0.93-1.06)	1,240	0.98 (0.93-1.04)
Yes	441	1.16 (1.05-1.26)	248	1.21 (1.07-1.35)	153	1.31 (1.09-1.52)
Child labour						
No	906	1.00 (0.94-1.07)	993	1.00 (0.93-1.06)	1,131	1.00 (0.94-1.06)
Yes	423	1.12 (1.02-1.22)	276	1.18 (1.04-1.32)	263	1.09 (0.94-1.23)
Poor family economic environment						
No	1,087	1.00 (0.94-1.06)	1,070	1.01 (0.95-1.07)	1,225	0.99 (0.93-1.05)
Yes	238	1.22 (1.06-1.37)	203	1.15 (1.00-1.31)	177	1.20 (1.03-1.36)
Serious illness or accident						
No	1,101	1.00 (0.94-1.06)	1,029	0.99 (0.93-1.05)	1,155	0.98 (0.92-1.04)
Yes	206	1.25 (1.09-1.42)	222	1.23 (1.08-1.38)	230	1.25 (1.09-1.41)
Stressful life events						
0	439	0.89 (0.80-0.98)	509	0.96 (0.88-1.04)	573	0.88 (0.80-0.97)
1	439	1.08 (0.98-1.18)	359	1.03 (0.92-1.14)	423	0.97 (0.87-1.07)
≥2	428	1.16 (1.05-1.27)	370	1.15 (1.04-1.27)	360	1.28 (1.16-1.40)

CI=confidence interval

Supplementary Table S4. Sensitivity analysis 1: Associations between childhood adversity and multimorbidity in older age (without depression)

	N	Number of comorbidities	Separate models [a]		Mutually adjusted model [b]	
			Model 1 [c]	Model 2 [d]	Model 1 [c] (N=3,646)	Model 2 [d] (N=3,311)
Premature birth		**Mean (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
No	3,679	0.98 (0.95-1.01)	Ref.	Ref.	Ref.	Ref.
Yes	181	1.04 (0.89-1.19)	1.16 (0.83-1.61)	1.09 (0.76-1.56)	1.09 (0.77-1.54)	1.03 (0.71-1.50)
Food restrictions						
No	3,140	0.94 (0.91-0.98)	Ref.	Ref.	Ref.	Ref.
Yes	842	1.14 (1.07-1.22)	1.39 *** (1.17-1.65)	1.30 * (1.07-1.58)	1.22 * (1.00-1.49)	1.22 (0.98-1.52)
Child labour						
No	3,030	0.96 (0.92-0.99)	Ref.	Ref.	Ref.	Ref.
Yes	962	1.07 (1.00-1.14)	1.24 * (1.05-1.46)	1.07 (0.88-1.31)	1.16 (0.97-1.39)	1.00 (0.81-1.24)
Poor family economic environment						
No	3,382	0.96 (0.92-0.99)	Ref.	Ref.	Ref.	Ref.
Yes	618	1.13 (1.04-1.22)	1.26 * (1.04-1.52)	1.09 (0.88-1.35)	1.01 (0.81-1.26)	0.95 (0.74-1.21)
Serious illness or accident						
No	3,285	0.94 (0.91-0.97)	Ref.	Ref.	Ref.	Ref.
Yes	658	1.19 (1.10-1.28)	1.69 *** (1.42-2.03)	1.59 *** (1.31-1.94)	1.61 *** (1.33-1.95)	1.54 *** (1.25-1.89)
Stressful life events						
0	1,521	0.88 (0.83-0.93)	Ref.	Ref.	Ref.	Ref.
1	1,221	0.98 (0.92-1.04)	1.20 * (1.00-1.43)	1.16 (0.95-1.41)	1.13 (0.94-1.36)	1.13 (0.92-1.38)
≥2	1,158	1.13 (1.07-1.19)	1.71 *** (1.44-2.03)	1.52 *** (1.25-1.84)	1.48 *** (1.23-1.79)	1.38 ** (1.12-1.70)
Model fit						
Likelihood ratio χ^2					68.2	225.5
P					<0.001	<0.001
AIC					4120	3592
BIC					4188	3745

[a] childhood adversity indicators in separate models; [b] childhood adversity indicators mutually adjusted

[c] adjusted for sex and cohort; [d] adjusted for sex, cohort, depression and covariates (socioeconomic status, behaviours and stressful life events in adulthood).

OR=odds ratio; CI=confidence interval; AIC=Akaike information criterion; BIC=Bayesian information criterion; * P<0.05; ** P<0.01; *** P<0.001

Supplementary Table S5. Sensitivity analysis 2A: Associations between childhood adversity and multimorbidity in older age (sampling weights)

	N	Number of comorbidities	Separate models [a]		Mutually adjusted model [b]	
			Model 1 [c]	Model 2 [d]	Model 1 [c] (N=3,581)	Model 2 [d] (N=3,421)
Premature birth		**Mean (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
No	3,679	1.02 (0.99-1.06)	Ref.	Ref.	Ref.	Ref.
Yes	181	1.11 (0.95-1.27)	1.15 (0.83-1.61)	1.07 (0.76-1.52)	1.08 (0.77-1.53)	1.02 (0.72-1.46)
Food restrictions						
No	3,140	0.99 (0.95-1.02)	Ref.	Ref.	Ref.	Ref.
Yes	842	1.19 (1.11-1.27)	1.30 ** (1.09-1.55)	1.22 (1.00-1.49)	1.14 (0.94-1.39)	1.12 (0.90-1.40)
Child labour						
No	3,030	1.00 (0.96-1.04)	Ref.	Ref.	Ref.	Ref.
Yes	962	1.11 (1.04-1.19)	1.25 ** (1.06-1.48)	1.11 (0.92-1.35)	1.20 * (1.00-1.44)	1.07 (0.86-1.31)
Poor family economic environment						
No	3,382	1.00 (0.96-1.03)	Ref.	Ref.	Ref.	Ref.
Yes	618	1.18 (1.09-1.28)	1.22 * (1.01-1.48)	1.06 (0.86-1.31)	0.98 (0.78-1.23)	0.93 (0.73-1.19)
Serious illness or accident						
No	3,285	0.98 (0.95-1.02)	Ref.	Ref.	Ref.	Ref.
Yes	658	1.24 (1.15-1.33)	1.64 *** (1.37-1.97)	1.52 *** (1.25-1.84)	1.55 *** (1.28-1.87)	1.46 *** (1.19-1.79)
Stressful life events						
0	1,521	0.91 (0.86-0.96)	Ref.	Ref.	Ref.	Ref.
1	1,221	1.03 (0.97-1.09)	1.20 * (1.01-1.44)	1.17 (0.96-1.41)	1.13 (0.94-1.36)	1.13 (0.93-1.38)
≥2	1,158	1.18 (1.11-1.25)	1.73 *** (1.45-2.05)	1.56 *** (1.28-1.89)	1.52 *** (1.26-1.83)	1.42 ** (1.16-1.75)

[a] childhood adversity indicators in separate models; [b] childhood adversity indicators mutually adjusted

[c] adjusted for sex and cohort; [d] adjusted for sex, cohort and covariates (socioeconomic status, behaviours and stressful life events in adulthood).

OR=odds ratio; CI=confidence interval; * P<0.05; ** P<0.01; *** P<0.001

Supplementary Table S6. Sensitivity analysis 2B: Associations between childhood adversity and multimorbidity in older age (multiple imputations)

	%	Number of comorbidities	Separate models [a]		Mutually adjusted model [b]	
			Model 1 [c]	Model 2 [d]	Model 1 [c] (N=4,731)	Model 2 [d] (N=4,731)
Premature birth		**Mean (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
No	95.5%	1.06 (1.02-1.09)	Ref.	Ref.	Ref.	Ref.
Yes	4.5%	1.13 (0.97-1.29)	1.12 (0.81-1.54)	1.09 (0.78-1.52)	1.06 (0.76-1.47)	1.03 (0.74-1.44)
Food restrictions						
No	78.5%	1.01 (0.98-1.05)	Ref.	Ref.	Ref.	Ref.
Yes	21.5%	1.23 (1.15-1.30)	1.34 ** (1.14-1.59)	1.22 * (1.02-1.47)	1.13 (0.94-1.36)	1.11 (0.91-1.35)
Child labour						
No	74.7%	1.03 (0.99-1.06)	Ref.	Ref.	Ref.	Ref.
Yes	25.3%	1.16 (1.09-1.23)	1.28 ** (1.09-1.50)	1.08 (0.91-1.29)	1.20 * (1.02-1.42)	1.03 (0.86-1.24)
Poor family economic environment						
No	84.1%	1.03 (0.99-1.06)	Ref.	Ref.	Ref.	Ref.
Yes	15.9%	1.22 (1.13-1.31)	1.25 * (1.04-1.51)	1.13 (0.93-1.38)	0.99 (0.81-1.22)	0.98 (0.79-1.21)
Serious illness or accident						
No	83.2%	1.02 (0.98-1.05)	Ref.	Ref.	Ref.	Ref.
Yes	16.8%	1.26 (1.18-1.35)	1.57 *** (1.31-1.88)	1.47 *** (1.22-1.78)	1.46 *** (1.21-1.75)	1.40 ** (1.15-1.69)
Stressful life events						
0	38.9%	0.94 (0.89-0.99)	Ref.	Ref.	Ref.	Ref.
1	31.1%	1.05 (0.99-1.11)	1.19 (1.00-1.41)	1.16 (0.97-1.39)	1.14 (0.95-1.36)	1.13 (0.94-1.35)
≥2	30.0%	1.21 (1.15-1.28)	1.68 *** (1.42-1.99)	1.51 *** (1.26-1.81)	1.54 *** (1.28-1.84)	1.43 *** (1.18-1.74)

[a] childhood adversity indicators in separate models; [b] childhood adversity indicators mutually adjusted

[c] adjusted for sex and cohort; [d] adjusted for sex, cohort and covariates (socioeconomic status, behaviours and stressful life events in adulthood).

OR=odds ratio; CI=confidence interval; * P<0.05; ** P<0.01; *** P<0.001