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AGEING AND MENTAL HEALTH. CHANGES SELF-REPORTED HEALTH DUE TO PHYSICAL ILLNESS AND MENTAL HEALTH STATUS IN AN AGEING COHORT.

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AGEING AND MENTAL HEALTH. CHANGES SELF-REPORTED HEALTH DUE TO PHYSICAL ILLNESS AND MENTAL HEALTH STATUS IN AN AGEING COHORT.

ABSTRACT

Objectives: We wished to examine how age transfers its effect to SRH through comorbid disease and mental illness and whether these processes have remained stable from 1986 until 2008. It is known that self-reported health (SRH) declines with increasing age, but also that comorbidity increases with age. The hypothesis is that ageing and/or the increased age-related burden of pathology explains the declining SRH.

Setting: The Tromsø Study (TS) is a cohort study utilizing a survey approach with repeated physical examinations. It was conducted in the municipality of Tromsø, Norway, from 1974 to 2008.

Participants: A total of 21199 women and 19229 men participated.

Primary and secondary outcome measures: SRH is the outcome of interest. We calculated and compared the effect sizes of age, comorbidity, and mental health symptoms utilizing multi-mediator analysis based on OLS regression.

Results: We found that ageing have a larger impact on SRH as compared to pathology. The direct effect of age represented 64-80% of the total effect while the total indirect effects of pathology represented 20-36%. Ageing became relatively less and less important, while physical illness emerged as increasingly important (from 15.7% to 41.2%). Age had by itself a protective effect on mental health symptoms and increasingly so (2.5% to 17.3%), but that mental health symptoms associated with physical illness increased the risk of low SRH (from 3.7% to 14.8%).

Conclusions: The results suggest that the effect on SRH of mental health symptoms caused by physical illness is an increasing public health problem. Treatment and care for specific medical conditions must therefore focus more strongly on how these conditions affect the patient's mental health and address these concerns accordingly.

Keywords: The Tromsø study, epidemiology, mental health, comorbid disease, self-reported health, ageing.

Strengths and limitations of this study:

- The sample comprises large, representative samples of a general population with repeated measures at appr. 7 years increments.
- Multi-mediator analysis allows for the interpretation of the joint effect of age, comorbid disease and mental health on self-reported health.
- We utilized the repeated measures as separate cross sectional data in the analysis.
- The first three panels (1974-1986) did not include any proper mental health symptoms measurement and was excluded, but the CONOR-MHI (1994) was validated against HSCL-10 and showed good agreement.

INTRODUCTION

Since medical treatment has improved over the last three decades with increased life expectancy, it seems timely to ask whether people's experiences of ageing, comorbid disease and mental health problems remain the same. Self-reported health (SRH) is a subjective assessment of current health status as seen by the patient or participant. It is well known that SRH declines with increasing age,[1-5] but is it ageing or the increased age-related burden of pathology that explains this association? The prevalence of coexisting chronic conditions is rising as life expectancy increases.[6] The age-specific decline could mean that the increasing level of pathology due to age explains this specific decline of SRH and not age by itself.

The Tromsø Study (TS) provides data that allows us to estimate the impact of a broad range of factors in a general population, utilizing surveys and physical examinations in a large representative sample.[7] We wished to examine how age transfers its effect on SRH through comorbid disease and mental health symptoms. Also, we wanted to explore how mental health symptoms are affected by physical disease and whether these processes have remained stable from 1986 until 2008.

METHOD

Sample and design

TS consists of six surveys conducted in Tromsø from 1974 to 2008.[7] The study population was recruited from all inhabitants in specific age groups. The aim has been to include large, representative samples of the Tromsø population, with the invitation of whole birth cohorts and random samples. The attendance rate was high (66-75%). A total of 21199 women and 19229 men gave informed signed consent and attended up to six separate health examinations. Tromsø 1 was a heart study conduced in 1974 and included only men aged 20-49. Tromsø 2 followed up the first study in 1979-80 but included both men aged 20-54 and women aged 20-49. Tromsø 3 was executed in 1986-87 and included men

and women with age range 20-56, and a 10% random selection of persons aged 12-19 as well as family (spouses and children) of those included in the family intervention project from 79-80. We excluded Tromsø 1-3. SRH was introduced during the 1980-ties; Tromsø 1-2 thus lack SRH and Tromsø 3 did not include any proper mental health symptoms measurement. Our samples starts with Tromsø 4 in 1994. It represents the largest wave and participants were followed up in 2001 and 2007/8.

Measurements

The participants completed a self-administrated questionnaire with questions on a broad range of diseases and symptoms, health behaviour, social conditions, education, financial situation and level of physical activity. *Self-Reported Health (SRH):* The independent variable SRH was reported by answering the question "What is your current state of health?" with answers ranging from very bad (0) to very good (4) in Tromsø 6, and from poor (1) to very good (4) in Tromsø 4 and 5. *Specific medical conditions:* We selected 13 symptomatic medical conditions reported in all panels. These were psoriasis, food allergies, chronic bronchitis, migraine, ulcer, asthma, thyroid, arthritis, myocardial infarction, cerebrovascular stroke, diabetes, osteoporosis, and angina. The conditions were self-reported by answering questions such as "Do you have or have you had....?" These were summarized into the variable Health Impact Index (HII), which considers both the severity and joint effects of the conditions.[4] Mental health symptoms were based on a well validated self-reported symptom inventory comprising questions that are representative of the symptom configurations of anxiety and depression commonly observed among outpatients.[8] The measurements used at T4, T5 and T6 have been compared with the Hopkins Symptom Checklist with reasonably good agreement.

Analysis

The purpose of the descriptive statistics was to define the distribution of SRH, comorbid disease and mental health across samples, age groups, and gender. We used cross tabulation and two-way ANOVA to describe the sample characteristics. *Multi-mediator analysis* was used for the analysis of the conditional nature of the mechanism by which age transmits its effect on SRH. The advantage of the method is that it allows for the interpretation of multiple confounders that may function as either mediators or moderators and interprets their joint effect on the statistical model derived from the theoretical model.[9, 10] The analytical goal of the multi-mediation analysis was to determine how age transfers its effect to SRH directly and through physical disease and mental illness. The first step is the conceptual model, which we based on the idea that age represents the timeline of life in which events like disease occur and physical condition changes. Previous analysis, tracking individual subjects, confirms that SRH decreases with increasing age and whenever levels of pathology increase. This implies that age might influence SRH either directly or indirectly through pathology as life events. The second step is to translate the conceptual model into a statistical model. Figre 1 shows the conceptual model and its translation into a statistical model.[11] The statistical model includes SRH as outcome (Y), age as main variable (X) with medical condition (M_1) and mental health symptoms (M_2) as mediators. Our statistical model includes three indirect effect lines (Figure 1).

- Ind1: Age→HII→SRH (a_1*b_1)
- Ind2: Age→HII→HSCL→SRH (a_1*d_{21}*b_2)
- Ind3: Age→HSCL→SRH (a_2*b_2)

We used multiple regression to assess the two mediators (M_1=Medical conditions and M_2= Mental health) and the reaction (Y=SRH). The regression coefficients, 95% confidence intervals, and model summary information for the mediated effect of age on self-reported health has been published as supplementary material (appendix 1).

(Insert Figure 1 here)

RESULTS

Characteristics and total effect of age

Table 1 shows the characteristics of the four samples indicating increasing comorbidity with a shift in 2001 (T5) when the comorbid levels decreased with a corresponding increase in SRH. Figure 2 shows profile plots for SHR, comorbidity and ratio of persons with sub-threshold and significant mental health symptoms across age and gender. Test for gender and age differences with two-way ANOVA show that all mean differences are significant ($p<.0001$) for SRH. Here, SRH declined significantly with increasing age with a corresponding increase in comorbidity at all three survey points. Although the gender differences were statistically significant for all three factors, the gender difference in SRH was less than a ten-year age difference in SRH in all surveys. For comorbidity, the gender difference was as large as a ten-year age difference for the two intermediate survey points, less so at the first and last where the gender difference was small. For comorbidity the most striking finding was the increase by age across all surveys, especially for women who have a increasingly greater burden of disease as they got older. For mental health symptoms, the greater burden for women is most striking.

Table 1. Distribution of SRH, physical condition and demographics, specific medical conditions, mental health symptoms and social context by sex, the Tromsø Studies in the period 1994-2008

	1994/5		2001		2007/8	
Self-Rated Health (Mean/SD.)	2.82	0.70	2.70	0.67	2.74	0.77
Comorbid disease (freq/col%)						
Not ill	15779	62 %	3648	46 %	5906	49 %
Mildly ill	6452	25 %	2360	30 %	3538	29 %
Moderately ill	2687	11 %	1477	19 %	1998	17 %
Seriously ill	621	2 %	423	5 %	636	5 %
Mental health symptoms (freq/col%)						
No symptoms	2061	8 %	2567	37 %	3769	33 %
Some symptoms	15751	64 %	2659	39 %	4363	38 %
Sub-threshold symptoms	4964	20 %	1187	17 %	2288	20 %
Significant symptoms	1762	7 %	464	7 %	985	9 %

(Insert Figure 1 here)

The total effect of age

We utilized an OLS regression model to determine the total effect of age on SRH. Table 2 shows the linear model of the total effect of age on Self-Reported Health. We see that age affected negatively on SRH in all samples, but also that the total effect of age attenuated from 1994 to 2008 in parallel with increasing life expectancy in the region. Each year of age represented -0.0175 (CI: -0.018, -0.017) deterioration of SRH in T4 but the effect dropped to -0.013 (CI: -0.014, -0.012) in T6.

Table 2. Linear model of the total effect of age on Self-Reported Health with 95% confidence intervals. Confidence intervals and Standard error are based on 1000 bootstrap samples.

	Tromsø 4			Tromsø 5			Tromsø 6		
	Coef.	[95% Conf.	Interval]	Coef.	[95% Conf.	Interval]	Coef.	[95% Conf.	Interval]
Age	-0.0175	-0.0181	-0.0170	-0.0146	-0.0157	-0.0136	-0.0128	-0.0139	-0.0117
Constant	3.6584	3.6311	3.6856	3.5742	3.5111	3.6372	3.4840	3.4179	3.5500

Note:	F(1, 25195) = 4039.67. P< 0.0001. R^2 = 0.1382	F(1, 7764) =783.57. P<0.0001. R^2 = 0.0917	F(1, 11962) = 519.36. P< 0.0001. R^2 = 0.0416

The indirect effect of pathology

The M_1 models in appendix 1 show that higher comorbidity was associated with increasing age in all waves (Coeff.=.050 in T4; .059 in T5; .050 in T6). The M_2 models show a significant effect for age on mental health symptoms (Coeff.= -0.0002 in T4; -0.0025 in T5; -0.0029 in T6), although medical conditions when they occurred affected mental health symptoms more than age (.030 in T4; .032 in T5; .041 in T6). All effect lines in the statistical model were estimated by series of OLS regression models (See Appendix 1 in the supplementary material). Table 3 shows the indirect and direct effects of age on SHR. We calculated these from the coefficients in appendix 1 according to our statistical model. Adding gender as a moderator on each effect line did not change the overall results.

Table 3 - Direct and indirect effect size with 95% bias corrected confidence intervals in parenthesis, standard error and ratio of indirect to direct effect of age on Self-reported health, Confidence intervals and Standard errors are based on 1000 bootstrap samples,

	Tromsø 4			**Tromsø 5**			**Tromsø 6**		
	Effect (95% CI)			Effect (95% CI)			Effect (95% CI)		
Total effect of Age on SRH:	**-0.0175**	-0.0181	-0.0170	**-0.0146**	-0.0157	-0.0136	**-0.0128**	-0.0139	-0.0117
Indirect effect of Age on SRH:									
Total:	**-0.0034**	-0.0032	-0.0037	**-0.0039**	-0.0034	-0.0043	**-0.0046**	-0.0040	-0.0052
Age→HII→SRH:	**-0.0027**	-0.0028	-0.0027	**-0.0043**	-0.0044	-0.0041	**-0.0053**	-0.0054	-0.0051
Age→HII→HSCL→SRH:	**-0.0006**	-0.0006	-0.0007	**-0.0013**	-0.0011	-0.0014	**-0.0019**	-0.0017	-0.0021
Age→HSCL→SRH:	**0.0000**	0.0002	-0.0002	**0.0016**	0.0021	0.0011	**0.0026**	0.0032	0.0020
Ratio of indirect to total effect of Age on SRH::									
Total:	**0.195**	0.176	0.215	**0.267**	0.217	0.318	**0.360**	0.284	0.442
Age→HII→SRH:	**0.157**	0.154	0.158	**0.290**	0.281	0.299	**0.412**	0.391	0.433
Age→HII→HSCL→SRH:	**0.037**	0.031	0.043	**0.086**	0.071	0.102	**0.148**	0.122	0.179
Age→HSCL→SRH:	**0.002**	-0.010	0.013	**-0.109**	-0.135	-0.083	**-0.200**	-0.229	-0.170

Note: Indirect effect of X on Y through Mi only = ai * bi, Indirect effect of X on Y through M1 and M2 in serial = a1 * d21 * b2, Direct effect of X on Y = c', The ratio of indirect effect to direct effect = Mi/c´(Figure 2 - statistical diagram). Note 2: *= Confidence Intervals includes zero.

We found that age had both a direct and indirect effect on SRH. The direct effect (c´) of age attenuated from 1994 to 2008 (T4: c' =-0.013, T5: c' = -0.011, T6: c' = -0.008). This suggests not only that age affected SRH independently of pathology even when controlling for the mediators, but also that age itself had lower impact on SRH at the latest measure point.

We found that age had an increasing negative indirect effect through comorbid diseases (T4: -0.0034; T5: -0.0035; T6: -0.0042). Since the total effect attenuated in the same period, this implied that the ratio of total to indirect effect of comorbid disease increased correspondingly more. It was 0.192 in 1994, 0.236 in 2001 and 0.330 in 2007/8. The trend implies that physical disease was an increasingly important factor relative to age itself to explain why SRH declines with increasing age.

The second indirect effect (Age→HII→HSCL→SRH) includes mental health symptoms associated with having a disease. We found a negative effect on SRH T4 of -0.0006, T5 of -0.0013 and T6 of -0.0019. This suggests that having a physical disease was associated with higher levels of mental health symptoms, which in turn affected SRH. The ratio of total to indirect effect of comorbid disease was -0.037 in T4, -0.086 in T5 and -0.148 in T6. Thus, we see a consistent increase in the relative size of the second indirect effect from 1994 to 2007/8. This implies that the relative significance of mental health issues connected to physical disease increased during this period, and at 14.8% of the total effect, it is also clinically significant.

The third indirect effect line (Age→HSCL→SRH) revealed that SRH increased with increasing age, which implies that mental health symptoms are associated with increasing age when controlled for physical disease. The ratio of effect size increased during this period from 0.002 in T4, -0.0109 in T5

and -0.200 in T6. This implies that when we disregard physical illness and mental health problems associated with these diseases, increasing age had a beneficial effect on SRH.

DISCUSSION

In this study, ageing affected SRH directly (72-80% of the total effect) and indirectly through increased levels of pathology (20-28%). We also observed a change in how the subjects reacted to ageing and physical illness. Ageing became relatively less and less important, while physical illness became increasingly significant (from 15.7% to 41.2%). Age by itself had a protective effect on mental health symptoms and increasingly so (2% to 20%), but mental health symptoms associated with physical illness represented an increasing risk (from 3.7% to 14.8%).

Physical illness is known to be related to mental health symptoms of anxiety and depression, which the HSCL-10 scale is especially sensitive to measure in a general population.[12] Epidemiological data suggests that severity of mental health symptoms is correlated with disease, e.g. one third of stroke survivors develop depression [13] and one quarter anxiety disorder;[14] Cardiovascular diseases have shown discrete effects for panic disorder and specific phobia.[15, 12] Older people with illnesses such as coronary heart disease, arthritis, and chronic lung disease show both increased levels of depressed mood and impaired well-being.[16] Cumulative stress exposure across different stress domains contributes to depressive symptoms in cancer survivors.[17] Moreover, pessimism, negative cancer-related rumination, and physical symptom distress predicted both anxiety and depression trajectories.

However, our findings indicate that physical illness in recent decades has been more strongly associated with mental health symptoms, i.e. the indirect effect on mental health symptoms via physical disease has increased over time. Accordingly, it seems plausible that physical diseases affect us more

than before, but also that they affect our reaction towards illness more than before. So, how can we explain these findings? Why does physical illness trigger symptoms of anxiety and depression more often than before?

One possible explanation may be found in social changes in Norway and the Norwegian healthcare system. Although we today have curative and palliative treatment of many more physical disorders, and more individuals have access to treatment, there is also an increased expectation of "active ageing" and living healthy lives.[18, 19] This expectation is realistic, as the incidence of especially cardiovascular diseases has been rapidly declining for several decades, but is contrasted by a decreasing case fatality, leaving more of those who still get cancer, coronary heart attacks and stroke with lasting disability as more people survive.[20] Furthermore, current healthcare services are organized to place greater emphasis on efficiency than on care and society has a faster pace of life, so that older people live more often alone and isolated than a few decades ago. From an evolutionary perspective, symptoms of anxiety and depression are understood as normal reactions to life-threatening and uncontrollable situations. For example, fear is an obvious adaptive function as it stimulates the "fight-or-flight" response when the individual is exposed to a threat or dangerous situation; unless the individual can escape, it will hide or "freeze" the situation.[21] Furthermore, Gilbert describes anxiety disorders as a maladaptive expression or phenotype of the original functional fear system where the acute stress response is triggered in an inappropriate manner.[22] Similarly, Nettle proposes that depression may represent a maladaptive expression of functional original control systems for positive affect, i.e., a dysfunctional downregulation of the positive affect system in certain situations and contexts.[23] Gilbert describes such a downregulation of positive affect as a defensive reaction, a similar fight-or-flight response, in situations where the individual experiences loss of control over aversive events or over significant resources including the social environment.[22]

Interestingly, we found that age was by itself protective of mental health symptoms when controlled for the mental health symptoms associated with physical illness. Several studies focus on how physical disease is associated with increased risk of mental health symptoms. In our study, this mechanism represented 4% of the total effect in 1986, 5% in 1994, 6% in 2001 and 12% in 2008. Our findings concur with studies on patient populations showing that mental health is an important aspect of health impairment when physical illness occurs.

Strengths and limitations of the method

Although measured on an ordinal scale, the underlying phenomenon of SRH is continuous, and the scales represent similar logical increments. Furthermore, the distribution of SRH, apart from being staggered, resembled the shape of a normal distribution. Hence, an OLS regression model could be used for the analysis of independent associations in the multivariable model.[9] Adding gender as a moderator on each effect line did not change the overall results. Mental health symptoms were measured with different instruments, which may affect our findings. T5 and T6 used the Hopkins Symptom Check List (HSCL-10) which is a self-reported symptom inventory comprising ten items representative of the symptom configurations of anxiety and depression commonly observed among outpatients.[8] T4 used the CONOR Mental Health Index (MHI). It was based on seven questions concerning different symptom configurations of anxiety and depression. It was partly derived from HSCL-10 and the General Health Questionnaire (GHQ). Fortunately, Tromsø 4 is included in the CONOR database that also included HSCL-10. The index has therefore been compared with HSCL-10 with a reasonably good agreement. They conclude that the scales can be used in epidemiological studies. For comparisons, they recommend to use the cut-off level of 2.15 for significant symptoms as equivalent to the 1.85 level in HSCL-10.[24, 25]

CONCLUSION

As medicine advances and life expectancy increases, we have higher expectations towards the healthcare system and to remain healthy even in old age. The results suggest that the effect on SRH due to mental health symptoms caused by physical illness is an increasing public health problem. It seems that our resilience when diseases occur is decreasing. This implies that treatment and care for specific medical conditions must focus more strongly on how these conditions affect the patient's mental health and address these concerns accordingly.

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CONTRIBUTOR STATEMENT

Profs Lorem, Schirmer and Emaus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lorem, Schirmer, and Emaus. Acquisition, analysis or interpretation of data: Lorem, Schirmer and Emaus. Statistical analysis: Lorem. Drafting of the manuscript: Lorem. Critical revision of the manuscript for important intellectual content: Lorem, Schirmer and Emaus. Administrative, technical or material support: The Tromsø Study of UiT The Arctic University of Norway provided the data. Conflict of interest disclosures: The authors declare no conflicts of interests. Funding/Support: UiT The Arctic University of Norway funded the study. Role of the funder/sponsor: The study sponsor had no role in the design and implementation of the study; collection, management, analysis, and interpretation

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DATA SHARING STATEMENT

We received the data from The Tromsø Study. The data contain sensitive health information about the participants. Data cannot be made publicly available without compromising participant confidentiality and privacy. Directives from the Research ethical committee and The Norwegian Data Protection Authority thus prohibits us from making the minimal data set publicly available. Data is available from The Tromsø study for researchers who meet the criteria for access to confidential data (https://en.uit.no/prosjekter/prosjekt?p_document_id=80172). Furhtermore, all variables are described in the NESSTAR database. http://tromsoundersokelsen.uit.no/webview/

COMPETING INTERESTS

Competing interests: None.

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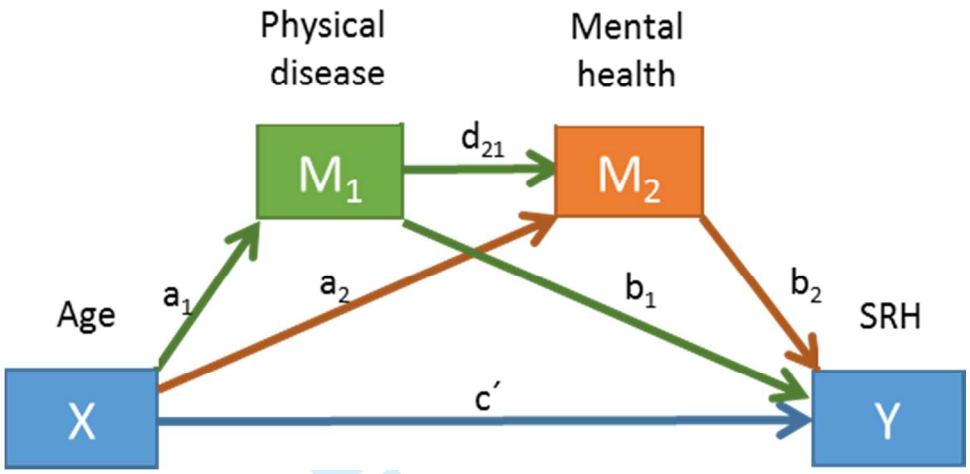
Figure 1 - conceptual and statistical diagram for the mediated effect of age on SRH through comorbid disease and mental health symptoms.

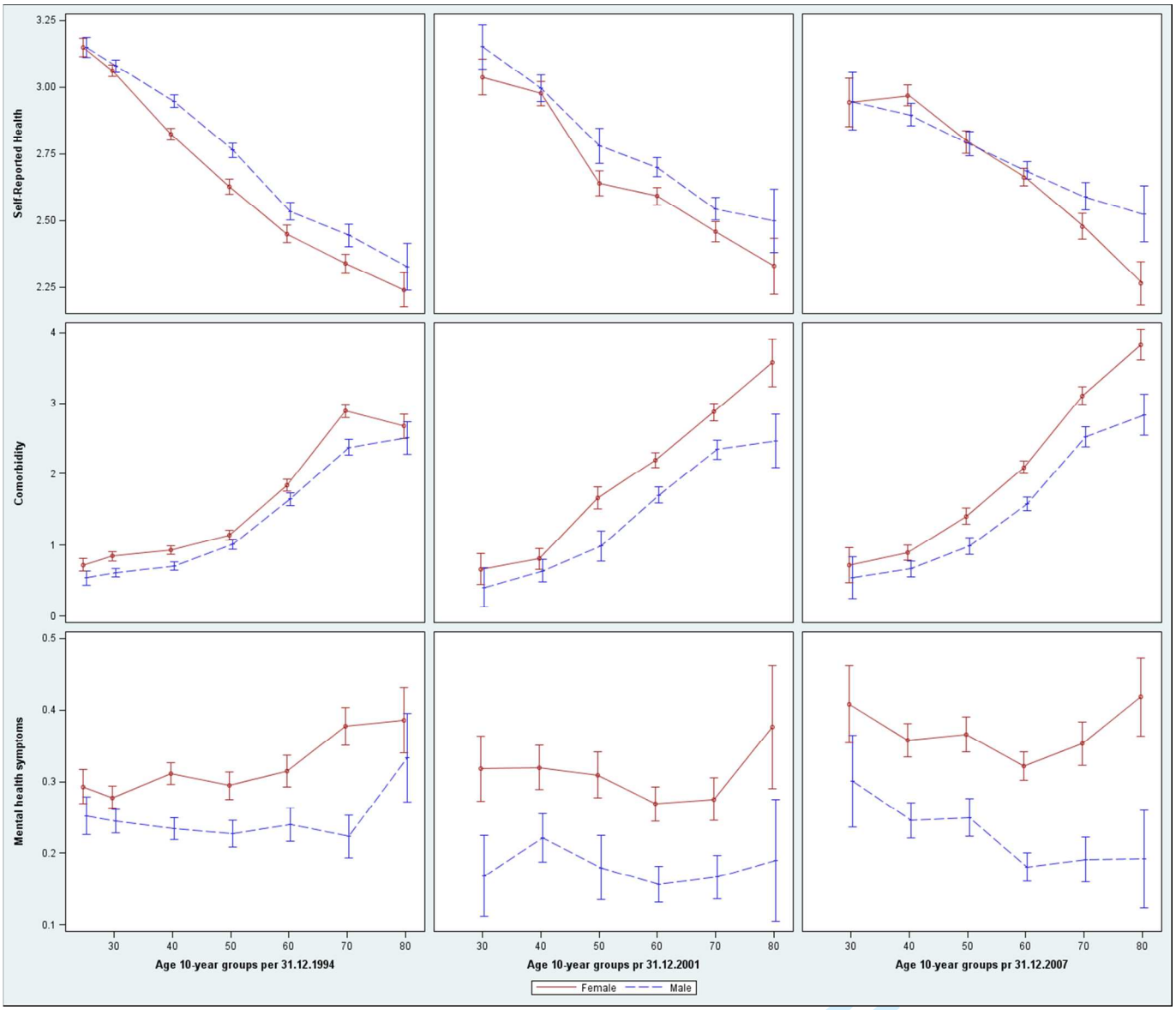


Indirect effect of X on Y through $M_i = a_i * b_i$

Indirekt effect of X on Y thorugh M_1 and M_2 in serial = $a_1 * d_{21} * b_2$

Direct effect of X on Y = c´

Figure 2. Profile plots for Self-Reported Health for interaction effects between age and gender with 95% confidence intervals.



Self-Reported Health: Range from very poor (0) to very good (4) in TS 6, and poor (1) to very good (4) in TS 4 and 5.
Comorbid disease: Number of diseases grouped into a score with range 0-17 (Mean .97) in TS 4, range 0-17 (Mean 1.59) in TS 5; and range 0-19 (Mean 1.53) in TS 6.
Mental health symptoms: CONOR-MHI with range 1-4 (Mean 1.52) in TS 4, and HSCL-10 with range 1-4 in TS 5 and 6 (mean 1.25 in TS 5 and mean 1.29 in TS 6).
All differences p <0.001. Red lines = women, Blue dotted lines = men, CI 95% is SE*1.96

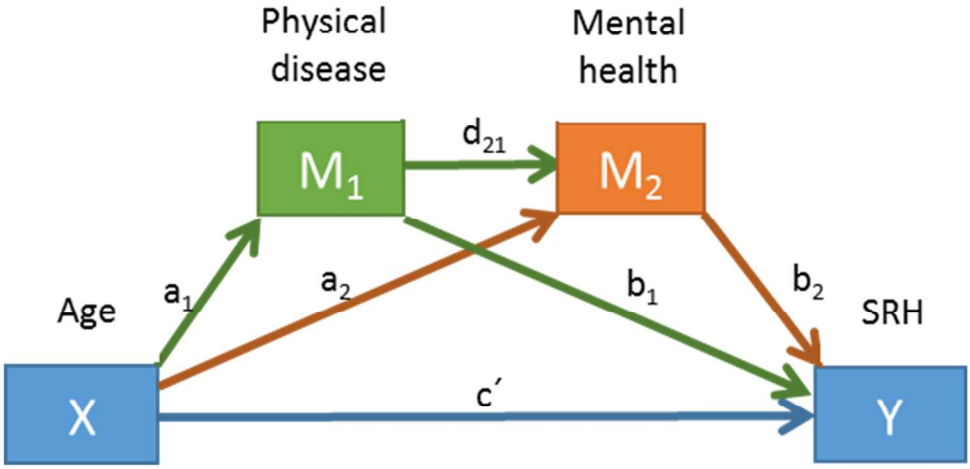
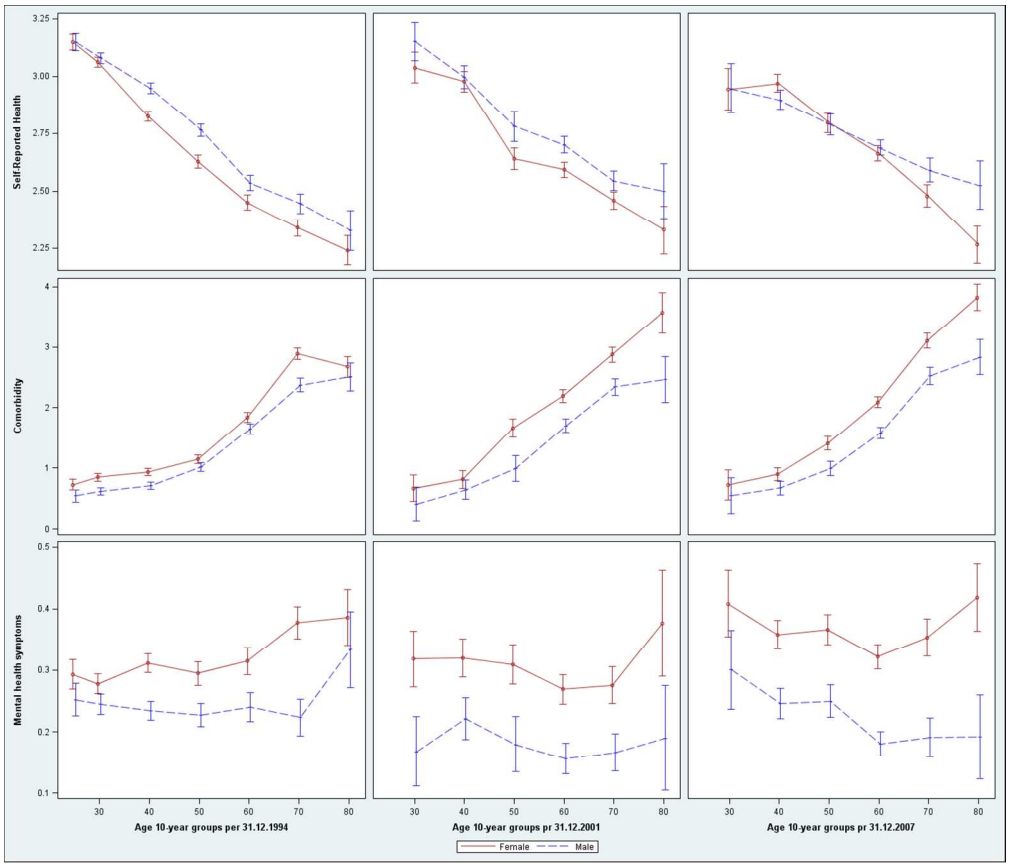


Figure 1 - conceptual and statistical diagram for the mediated effect of age on SRH through comorbid disease and mental health symptoms
(Insert Figure 1 here)
338x190mm (96 x 96 DPI)



Caption : Caption : Figure 2. Profile plots for Self-Reported Health for interaction effects between age and gender with 95% confidence intervals.
(Insert Figure 2 here)
355x304mm (100 x 100 DPI)

Appendix 1. Regression Coefficients with bias corrected Standard Errors for mediated effect of age on Self-reported health. Confidence intervals and Standard error are based on 1000 bootstrap samples.

Consequent 1994

		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff,	[95% Conf. Interval]			Coeff,	[95% Conf. Interval]			Coeff,	[95% Conf. Interval]	
Constant	i_{M1}	-0.733	-0.810	-0.656	i_{M2}	1.48526	1.467446	1.503073	i_y	4.421846	4.382292	4.461401
X (Age)	a_1	0.0390	0.037	0.041	a_2	0.000	-0.000315	0.0004202	c'	-0.014	-0.014472	-0.013333
M1 (Medical condition)		---	---	---	d_{12}	0.0297326	0.0262572	0.033208	b_1	-0.0704918	-0.074957	-0.066027
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.5594842	-0.57862	-0.540348
		R-squared = 0.1002				R-squared = 0.0169				R-squared = 0.2882		
		Wald $\chi2(1) = 1826.35$ p < .001				Wald $\chi2(2) = 309.30$, p<.001				Wald $\chi2(3) = 8907.28$, p < .001		

Consequent 2001

		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff,	[95% Conf. Interval]			Coeff,	[95% Conf. Interval]			Coeff,	[95% Conf. Interval]	
Constant	i_{M1}	-1.520	-1.677	-1.363	i_{M2}	1.341679	1.304584	1.378773	i_y	4.217373	4.13278	4.301967
X (Age)	a_1	0.0551	0.052	0.058	a_2	-0.003	-0.003269	-0.0020216	c'	-0.010	-0.011255	-0.009182
M1 (Medical condition)		---	---	---	d_{12}	0.0378559	0.03291	0.0428018	b_1	-0.0772212	-0.084309	-0.070134
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.6020822	-0.644952	-0.559213
		R-squared = 0.1180				R-squared = 0.0451				R-squared = 0.2734		
		Wald $\chi2(1) = 1339.28$ p < .001				Wald $\chi2(2) = 239.84$, p<.001				Wald $\chi2(3) = 2295.51$, p < .001		

Consequent 2007/8

		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff,	[95% Conf. Interval]			Coeff,	[95% Conf. Interval]			Coeff,	[95% Conf. Interval]	
Constant	i_{M1}	-2.020	-2.194	-1.847	i_{M2}	1.425522	1.388859	1.462185	i_y	5.278	5.197401	5.358518
X (Age)	a_1	0.0627	0.059	0.066	a_2	-0.0034595	-0.004095	-0.0028236	c'	-0.0075404	-0.00861	-0.006471
M1 (Medical condition)		---	---	---	d_{12}	0.0409442	0.0366294	0.0452591	b_1	-0.0843211	-0.091595	-0.077048
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.7412179	-0.77872	-0.703716
		R-squared = 0.1229				R-squared = 0.0471				R-squared = 0.2529		
		Wald $\chi2(1) = 1501.87$ p < .001				Wald $\chi2(2) = 358.15$ p<.001				Wald $\chi2(3) = 3165.11$, p < .001		

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Ageing and mental health: changes in self-reported health due to physical illness and mental health status with consecutive cross sectional analyses

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AGEING AND MENTAL HEALTH: CHANGES IN SELF-REPORTED HEALTH DUE TO PHYSICAL ILLNESS AND MENTAL HEALTH STATUS WITH CONSECUTIVE CROSS SECTIONAL ANALYSES

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ABSTRACT

Objectives: It is known that self-reported health (SRH) declines with increasing age, but also that comorbidity increases with age. We wished to examine how age transfers its effect to SRH through comorbid disease and mental illness and whether these processes remained stable from 1994 until 2008. The hypothesis is that ageing and/or the increased age-related burden of pathology explains the declining SRH.

Setting: The Tromsø Study (TS) is a cohort study utilizing a survey approach with repeated physical examinations. It was conducted in the municipality of Tromsø, Norway, from 1974 to 2008.

Participants: A total of 21199 women and 19229 men participated.

Primary and secondary outcome measures: SRH is the outcome of interest. We calculated and compared the effect sizes of age, comorbidity and mental health symptoms utilizing multi-mediator analysis based on OLS regression.

Results: Ageing had a negative impact on SRH, but the total effect of age decreased from 1994 to 2007. We assessed the direct effect of age, and then the proportion of indirect age related effects through physical illness and mental health symptoms on the total effect. The direct effect of age represented 79.3% of the total effect in 1994 and decreased to 58.8% in 2007. Physical illness emerged as an increasingly important factor and increased its influence from 15.7% to 41.2% of the total effect. Age alone had a protective effect on mental health symptoms and this increased (2.5% to 17.3%), but we found a stronger association between mental health symptoms and physical disease in the later waves of the study (increasing from 3.7% to 14.8%).

Conclusions: The results suggest that the effect on SRH of mental health symptoms caused by physical illness is an increasing public health problem. Treatment and care for specific medical

conditions must therefore focus more strongly on how these conditions affect the patient's mental health and address these concerns accordingly.

Keywords: The Tromsø study, epidemiology, mental health, comorbid disease, self-reported health, ageing.

Strengths and limitations of this study:

- The sample comprises large, representative samples of a general population with repeated measures at approximately seven-year intervals.
- Multi-mediator analysis allows for the interpretation of the joint effect of age, comorbid disease and mental health on self-reported health.
- We utilized the repeated measures as separate cross sectional data in the analysis.
- The first three panels (1974-1986) did not include any adequate measurement of mental health symptoms and were excluded, but the CONOR-MHI (1994) was validated against the Hopkins Symptom Checklist (HSCL) and showed good agreement.

INTRODUCTION

Self-reported health (SRH) is a subjective assessment of current health status as seen by the patient or participant. It is well known that a whole range of biological, psychological and socio-economic factors affect SRH, but also that these factors interact.[1-5] The research literature suggests that SRH is

produced in a cognitive process that is inherently subjective and contextual, but also that SRH predicts mortality and other health outcomes; this shows that the basis of self-rated health lies in the biological and physiological state of the individual organism.[6] Well-known crucial biological factors that independently affect SRH are specific medical conditions (e.g. cardiovascular diseases, diabetes and asthma) and health risk factors (e.g. resting heart rate, blood pressure, cholesterol, BMI, and endocrine measures). Although the effect of SRH attenuates when such variables are controlled for, SRH still remains as an independent variable for all-cause death and other future health outcomes.[7-11] Mental health symptoms affect SRH, but mental health is also affected by physical disease. The literature suggests that severity of mental health symptoms correlates with many specific medical conditions, and consequently with impaired well-being. Comorbid strain increases with increasing age, and older people are particularly at risk of experiencing anxiety and depression.[12-17]

To summarize, it is well-documented that SRH declines with increasing age but whether it is ageing alone or the increased age-related burden of pathology that explains this association is still unanswered. The prevalence of coexisting chronic conditions is rising as life expectancy increases in contemporary Western society.[18] The age-specific decline could mean that the increasing level of pathology due to age explains this specific decline of SRH and not ageing by itself.

There are to our knowledge no studies that describe the combined effect of ageing, comorbid physical disease and mental health symptoms on general perceived health status. Moreover, since medical treatment has improved over the last three decades, leading to increased life expectancy, it seems timely to ask whether people's experiences of ageing, comorbid disease and mental health problems remain the same. We wished to examine how age transfers its effect on SRH through comorbid physical disease and mental health symptoms. A further aim was to explore how mental health symptoms are affected by physical disease and whether these processes remained stable from 1986 until 2008.

METHOD

Sample and design

The Tromsø Study (TS) was a cohort study which provided data allowing us to estimate the impact of a broad range of factors on a general population, utilizing surveys and physical examinations in a large representative sample.[19] TS consisted of six surveys conducted in Tromsø in Northern Norway from 1974 to 2008. We utilized consecutive cross sectional analyses within the Tromsø Study. The study population was recruited from all inhabitants in specific age groups. The aim was to include large, representative samples of the Tromsø population, with the invitation of whole birth cohorts and random samples. The attendance rate was high (66-75%). A total of 21199 women and 19229 men gave informed signed consent and attended up to six separate health examinations. Tromsø 1 was a heart study conducted in 1974 and included only men aged 20-49. Tromsø 2 followed up the first study in 1979-80 but included both men (aged 20-54) and women (aged 20-49). Tromsø 3 was executed in 1986-87 and included men and women in the 20-56 age range, and a 10% random selection of persons aged 12-19. We excluded Tromsø 1-3. SRH was introduced during the 1980s; Tromsø 1and 2 thus lack SRH and Tromsø 3 did not include any adequate measurement of mental health symptoms. Our sample starts with Tromsø 4 in 1994. Tromsø 4 is the largest wave and participants were followed up in 2001 and 2007/8. We excluded those with missing data (n=736 in TS4, n=1132 in TS5, n=767 in TS6). The final analysis therefore comprised 12408 men and 13579 women from TS4, 3108 men and 3746 women from TS5, and 5769 men and 6338 women from TS6.

Measurements

The participants completed a self-administrated questionnaire with questions on a broad range of diseases and symptoms, health behaviour, social conditions, education, financial situation and level

of physical activity. *Self-Reported Health (SRH):* The independent variable SRH was reported by answering the question "What is your current state of health?" with answers ranging from very bad (0) to very good (4) in Tromsø 6, and from poor (1) to very good (4) in Tromsø 4 and 5. *Specific medical conditions:* We selected 13 symptomatic medical conditions reported in all panels. These were psoriasis, food allergies, chronic bronchitis, migraine, ulcer, asthma, thyroid disease, arthritis, myocardial infarction, cerebrovascular stroke, diabetes, osteoporosis, and angina. The conditions were self-reported by answering questions such as "Do you have or have you had....?" We utilized the Health Impact Index (HII) to measure the comorbid conditions. Diseases have a varied impact on SRH. HII classifies patients with comorbid disease according to the impact that each condition has on SRH by assigning a weight for each condition. HII equals the total score of each condition of the participant. HII thus considers both the severity and joint effects of the conditions.[4] The range was 0-18 in TS4, 0-17 in TS5 and 0-22 in TS 6. Appendix 1 shows the conditions included with their weights and prevalence in the different waves.

Mental health symptoms were based on a well validated self-report symptom inventory comprising questions representative of the symptom configurations of anxiety and depression commonly observed among outpatients.[20] It includes questions such as "Have you experienced sudden fear without apparent reason", "…felt tense or upset", "…easily blamed yourself", "…felt depressed or sad", "…felt useless or worthless", "…felt that everything is a struggle" or "…felt hopelessness". Each answer is scored from 1 to 4. The measurement is the average score. The range was therefore 1-4 in all waves. The measurements used at T4, T5 and T6 have been compared with the Hopkins Symptom Checklist (HSCL) with reasonably good agreement.[21]

Analysis

The purpose of the descriptive statistics was to define the distribution of SRH, comorbid disease and mental health across samples, age groups, and gender. We used cross tabulation and two-way ANOVA to describe the characteristics of the sample. *Multi-mediator analysis* was used for the analysis of the conditional nature of the mechanism by which age transmits its effect on SRH. The advantage of this method is that it allows for the interpretation of multiple confounders that may function as either mediators or moderators and interprets their joint effect on the statistical model derived from the theoretical model.[22, 23] The analytical goal of the multi-mediation analysis was to determine how age transfers its effect to SRH directly and through physical disease and mental illness. The first step was the conceptual model, which we based on the idea that age represents the timeline of life in which events like disease occur and physical condition changes. Previous analysis, tracking individual subjects, confirms that SRH decreases with increasing age and whenever levels of pathology increase. This implies that age might influence SRH either directly or indirectly through pathology as life events. The second step was to translate the conceptual model into a statistical model. Figure 1 shows the conceptual model and its translation into a statistical model.[24] The statistical model includes SRH as outcome (Y), age as the main variable (X) with medical condition (M_1) and mental health symptoms (M_2) as mediators. Our statistical model includes three indirect effect lines (Ind 1-3).

- Ind 1: Age→HII→SRH (a_1*b_1)
- Ind 2: Age→HII→HSCL→SRH (a_1*d_{21}*b_2)
- Ind 3: Age→HSCL→SRH (a_2*b_2)

We used multiple regression to assess the two mediators (M_1=Medical conditions and M_2= Mental health) and the reaction (Y=SRH). The regression coefficients, 95% confidence intervals, and model summary information for the mediated effect of age on self-reported health have been published as supplementary material (Appendix 2).

(Insert Figure 1 here)

RESULTS

Characteristics and total effect of age

Table 1 shows the characteristics of the four samples indicating increasing comorbidity with a shift in 2001 (T5) when the comorbid levels decreased with a corresponding increase in SRH. Figure 2 shows profile plots for SRH, comorbidity and ratio of persons with sub-threshold and significant mental health symptoms across age and gender. Testing for gender and age differences with two-way ANOVA showed that all mean differences were significant ($p<.0001$) for SRH. Here, SRH declined significantly with increasing age with a corresponding increase in comorbidity at all three survey points. Although the gender differences were statistically significant for all three factors, the gender difference in SRH was less than a ten-year age difference in SRH in all surveys. For comorbidity, the gender difference was as large as a ten-year age difference for the two intermediate survey points, but less so at the first and last where the gender difference was small. For comorbidity, the most striking finding was the increase by age across all surveys, especially for women, who had an increasing burden of disease as they got older. For mental health symptoms, the greater burden for women was most striking.

Table 1. Distribution of SRH, physical condition and demographics, specific medical conditions, mental health symptoms and social context by gender in Tromsø 4-6 (1994-2008)

	Tromsø 4		Tromsø 5		Tromsø 6	
Self-Rated Health (Mean/SD)	2.82	(0.70)	2.7	(0.67)	2.74	(0.77)
Age (Mean/SD)	48.1	(14.8)	60.1	(13.8)	58.7	(12.4)
Health impact index (Mean/SD)	0.95	(1.66)	1.72	(2.18)	1.66	(2.21)
Mental health symptoms (Mean/SD)	1.25	(0.36)	1.29	(0.38)	1.52	(0.41)

(Insert Figure 2 here)

The total effect of age

We utilized an OLS regression model to determine the total effect of age on SRH. Table 2 shows the linear model of the total effect of age on SRH. We see that age had a negative effect on SRH in all samples, but also that the total effect of age attenuated from 1994 to 2008 in parallel with increasing life expectancy in the region. Each year of age represented -0.0175 (CI: -0.018, -0.017) deterioration of SRH in T4 but the effect dropped to -0.013 (CI: -0.014, -0.012) in T6.

Table 2. Linear model of the total effect of age on Self-Reported Health with 95% confidence intervals. Confidence intervals and standard errors are based on 1000 bootstrap samples.

	Tromsø 4			Tromsø 5			Tromsø 6		
	Coeff.	[95% CI)		Coeff.	[95% CI)		Coeff.	[95% CI)	
Age	-0.0175	-0.0181	-0.0170	-0.0146	-0.0157	-0.0136	-0.0128	-0.0139	-0.0117
Constant	3.6584	3.6311	3.6856	3.5742	3.5111	3.6372	3.4840	3.4179	3.5500
Note:	$F(1, 25195) = 4039.67$. $P< 0.0001$. $R^2 = 0.1382$			$F(1, 7764) = 783.57$. $P<0.0001$. $R^2 = 0.0917$			$F(1, 11962) = 519.36$. $P< 0.0001$. $R^2 = 0.0416$		

The indirect effect of pathology

The M_1 models in Appendix 2 show that higher comorbidity was associated with increasing age in all waves (Coeff.=.050 in T4; .059 in T5; .050 in T6). The M_2 models show a significant effect for age on mental health symptoms (Coeff.= -0.0002 in T4; -0.0025 in T5; -0.0029 in T6), although medical conditions when they occurred affected mental health symptoms more than age (.030 in T4; .032 in T5; .041 in T6). All effect lines in the statistical model were estimated by series of OLS regression models (see Appendix 2 in the supplementary material). Table 3 shows the indirect and direct effects of age on SHR. We calculated these from the coefficients in Appendix 2 according to our statistical model. Adding gender as a moderator on each effect line did not change the overall results.

Table 3. Direct and indirect effect size with 95% bias corrected confidence intervals in parentheses, standard errors and ratio of indirect to direct effect of age on self-reported health. Confidence intervals and standard errors are based on 1000 bootstrap samples.

	Tromsø 4			Tromsø 5			Tromsø 6		
	Effect (95% CI)			Effect (95% CI)			Effect (95% CI)		
Total effect of age on SRH:	**-0.0175**	-0.0181	-0.0170	**-0.0146**	-0.0157	-0.0136	**-0.0128**	-0.0139	-0.0117
Indirect effect of age on SRH:									
Total:	**-0.0034**	-0.0032	-0.0037	**-0.0039**	-0.0034	-0.0043	**-0.0046**	-0.0040	-0.0052
Age→HII→SRH:	**-0.0027**	-0.0028	-0.0027	**-0.0043**	-0.0044	-0.0041	**-0.0053**	-0.0054	-0.0051
Age→HII→HSCL→SRH:	**-0.0006**	-0.0006	-0.0007	**-0.0013**	-0.0011	-0.0014	**-0.0019**	-0.0017	-0.0021
Age→HSCL→SRH:	**0.000***	0.0002	-0.0002	**0.0016**	0.0021	0.0011	**0.0026**	0.0032	0.0020
Ratio of indirect to total effect of age on SRH:									
Total:	**0.195**	0.176	0.215	**0.267**	0.217	0.318	**0.360**	0.284	0.442
Age→HII→SRH:	**0.157**	0.154	0.158	**0.290**	0.281	0.299	**0.412**	0.391	0.433
Age→HII→HSCL→SRH:	**0.037**	0.031	0.043	**0.086**	0.071	0.102	**0.148**	0.122	0.179
Age→HSCL→SRH:	**0.002***	-0.010	0.013	**-0.109**	-0.135	-0.083	**-0.200**	-0.229	-0.170

Note: Indirect effect of X on Y through Mi only = ai * bi, Indirect effect of X on Y through M1 and M2 in serial = a1 * d21 * b2, Direct effect of X on Y = c', The ratio of indirect effect to direct effect = Mi/c´(Figure 1 - statistical diagram). Note 2: *= Confidence intervals include zero.

We found that age had both a direct and indirect effect on SRH. The direct effect (c´) of age attenuated from 1994 to 2008 (T4: c' =-0.013, T5: c' = -0.011, T6: c' = -0.008). This suggests not only that age affected SRH independently of pathology even when controlling for the mediators, but also that age itself had a lower impact on SRH at the latest measuring point.

We found that age had an increasing negative indirect effect through comorbid diseases (T4: -0.0034; T5: -0.0035; T6: -0.0042). Since the total effect attenuated in the same period, this implied that the ratio of total to indirect effect of comorbid disease increased correspondingly more. It was 0.192 in 1994, 0.236 in 2001 and 0.330 in 2007/8. This trend implied that physical disease was an increasingly important factor relative to age itself to explain why SRH declines with increasing age.

The second indirect effect (Age→HII→HSCL→SRH) included mental health symptoms associated with having a disease. We found a negative effect on SRH T4 of -0.0006, T5 of -0.0013 and T6 of -0.0019. This suggests that having a physical disease was associated with higher levels of mental health symptoms, which in turn affected SRH. The ratio of total to indirect effect of comorbid disease was -0.037 in T4, -0.086 in T5 and -0.148 in T6. Thus, we see a consistent increase in the relative size of the second indirect effect from 1994 to 2007/8. This implied that the relative significance of mental health issues connected to physical disease increased during this period, and at 14.8% of the total effect, it is also clinically significant.

The third indirect effect line (Age→HSCL→SRH) revealed that SRH increased with increasing age, which implies that mental health symptoms are associated with increasing age when controlled for physical disease. The ratio of effect size increased during this period from 0.002 in T4 to -0.0109 in T5 and -0.200 in T6. This implied that when we disregard physical illness and mental health problems associated with physical illness, increasing age had a beneficial effect on SRH.

DISCUSSION

Ageing affected self-reported health (SRH) directly and also indirectly through increased levels of pathology. We observed a change in how ageing and physical disease influenced SRH between the different waves. The direct effect of ageing (c') represented 79.3% of the total effect in 1994, 69.8% in 2001, and 58.8% in 2007/8. This means that ageing is still the most important factor for SRH, but that ageing itself became relatively less important between the waves. Meanwhile, physical disease became an increasingly important factor for SRH. As shown in Table 3, comorbid conditions (HII) represented 15.7% of the total effect in 1994, 26.7% in 2001, and 41.2% in the last wave in 2007/8. Furthermore, ageing itself had a protective effect on mental health symptoms which increased (2.0% to 20.0% of the

total effect). We found a stronger association between mental health symptoms and physical disease in the later waves (increasing from 3.7% to 14.8%). Mental health symptoms related to physical disease consequently led to lower SRH levels in the later parts of the study.

Physical disease is known to be related to mental health symptoms of anxiety and depression, which the HSCL-10 scale is especially sensitive to measure in a general population.[15] Epidemiological data suggest that severity of mental health symptoms correlates with disease, e.g. one third of stroke survivors develop depression [12] and one quarter anxiety disorders.[13] Cardiovascular diseases have shown discrete effects for panic disorder and specific phobia.[14, 15] Older people with illnesses such as coronary heart disease, arthritis, and chronic lung disease show both increased levels of depressed mood and impaired well-being.[16] Cumulative stress exposure across different stress domains contributes to depressive symptoms in cancer survivors.[17] Moreover, pessimism, negative cancer-related rumination, and physical symptom distress predicted both anxiety and depression trajectories.

However, our findings indicate that physical disease in recent decades has become more strongly associated with mental health symptoms, i.e. the indirect effect on mental health symptoms via physical disease has increased over time. Accordingly, it seems plausible that physical diseases in terms of SRH affect us more than before, but also that physical disease has a greater impact on our reaction towards illness than before. So, how can we explain these findings? Why does physical disease trigger symptoms of anxiety and depression more often than before?

One possible explanation may be found in social changes in Norway and the Norwegian healthcare system. Although we today have curative and palliative treatment of many more physical disorders, and more individuals have access to treatment, there is also an increased expectation of "active ageing" and healthy living.[25, 26] This expectation is realistic, as the incidence of especially cardiovascular diseases has been rapidly declining for several decades, but is contrasted by a

decreasing case fatality, leaving more of those who still get cancer, coronary heart attacks and stroke with lasting disability as more people survive.[27]

SRH can reflect the states of the human body and mind. People base their health assessments on different types of information and contextual frameworks.[6] It is plausible that people who expect to age actively become unhappy or worried when encountering limitations and disease. It may also be argued that people tend to respond negatively to questions on their health or limitations when comparing their situation with others at similar age. Bodily sensations that are directly available to the individual are another source of information.[6] Accordingly, it seems plausible that people compare current body status with the situation before the disease occurred, and experience fear of relapse or having another disease. We cannot answer this assumption based on three cross-sectional analyses; however, it is a hypothesis that could be answered by tracking individuals in the Tromsø study cohort.

Furthermore, current healthcare services are organized to place greater emphasis on efficiency than on care, and society has a faster pace of life so that older people live more often alone and isolated than a few decades ago. From an evolutionary perspective, symptoms of anxiety and depression are understood as normal reactions to life-threatening and uncontrollable situations. For example, fear is an obvious adaptive function as it stimulates the "fight-or-flight" response when the individual is exposed to a threat or dangerous situation; unless the individual can escape, it will hide or "freeze" the situation.[28] Furthermore, Gilbert describes anxiety disorders as a maladaptive expression or phenotype of the original functional fear system where the acute stress response is triggered in an inappropriate manner.[29] Similarly, Nettle proposes that depression may represent a maladaptive expression of an original functional control system for positive affect, i.e., a functional downregulation of positive affect in certain situations and contexts.[30] Gilbert describes such a downregulation of positive affect as a defensive reaction, a similar fight-or-flight response, in situations where the individual experiences loss of control over aversive events or over significant resources including the

social environment.[29] An increased incidence of comorbid physical disorders with consequent reduced access to social participation can thus be a plausible explanation of an increase in mental symptoms related to physical disorders.

Interestingly, we found that age by itself was protective of mental health symptoms when controlled for the mental health symptoms associated with physical illness. Several studies focus on how physical disease is associated with increased risk of mental health symptoms. In our study, this mechanism represented 4% of the total effect in 1986, 5% in 1994, 6% in 2001 and 12% in 2008. Our findings concur with studies on patient populations showing that mental health is an important aspect of impairment of SRH when physical illness occurs.

Strengths and limitations of the method

HII includes 13 symptomatic medical conditions, but does not include risk factors such as hypertension or dyslipidemia. These could be included as mediators on the age->HII->SRH effect line, but this did not change the overall findings of the model. The Tromsø study includes cancer but it is self-reported and does not distinguish between those with an active illness and those who have had cancer. That was the most likely explanation for why it did not add to the model[4] and it was therefore not included.

Although measured on an ordinal scale, the underlying phenomenon of SRH is continuous, and the scales represent similar logical increments. Furthermore, the distribution of SRH, apart from being staggered, resembled the shape of a normal distribution. Hence, an OLS regression model could be used for the analysis of independent associations in the multivariable model.[22] Adding gender as a moderator on each effect line did not change the overall results. Mental health symptoms were measured with different instruments, which may have affected our findings. T5 and T6 used the Hopkins Symptom Check List (HSCL-10), which is a self-reported symptom inventory comprising ten

items representative of the symptom configurations of anxiety and depression commonly observed among outpatients.[20] T4 used the CONOR Mental Health Index (MHI). This was based on seven questions concerning different symptom configurations of anxiety and depression. It was partly derived from HSCL-10 and the General Health Questionnaire (GHQ). Fortunately, Tromsø 4 is included in the CONOR database that also included HSCL-10. The index has therefore been compared with HSCL-10 with reasonably good agreement. It has been concluded that the scales can be used in epidemiological studies. For comparisons, it is recommended to use the cut-off level of 2.15 for significant symptoms as equivalent to the 1.85 level in HSCL-10.[21, 31]

CONCLUSION

As medicine advances and life expectancy increases, we have higher expectations for the healthcare system and to remain healthy even in old age. The results suggest that the effect on SRH of mental health symptoms caused by physical illness is an increasing public health problem. It seems that our resilience to diseases is decreasing. Therefore, treatment and care for specific medical conditions must focus more strongly on how these conditions affect the patient's mental health and address these concerns accordingly.

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CONTRIBUTOR STATEMENT

Profs Lorem, Schirmer, Wang and Emaus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lorem, Schirmer, and Emaus. Acquisition, analysis or interpretation of data: Lorem, Schirmer, Wang and Emaus. Statistical analysis: Lorem. Drafting of the manuscript: Lorem. Critical revision of the manuscript for important intellectual content: Lorem, Schirmer, Wang and Emaus. Administrative, technical or material support: The Tromsø Study of UiT The Arctic University of Norway provided the data. Conflict of interest disclosures: The authors declare no conflicts of interests. Funding/Support: UiT The Arctic University of Norway funded the study. Role of the funder/sponsor: The study sponsor had no role in the design and implementation of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication. Obtained funding: Emaus.

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DATA SHARING STATEMENT

We received the data from the Tromsø study. The data contain sensitive health information about the participants. Data cannot be made publicly available without compromising participant confidentiality and privacy. Directives from the Research Ethical Committee and the Norwegian Data Protection Authority thus prohibit us from making the minimal data set publicly available. Data is available from the Tromsø study for researchers who meet the criteria for access to confidential data (https://en.uit.no/prosjekter/prosjekt?p_document_id=80172). Furthermore, all variables are described in the NESSTAR database: http://tromsoundersokelsen.uit.no/webview/

COMPETING INTERESTS

Competing interests: None.

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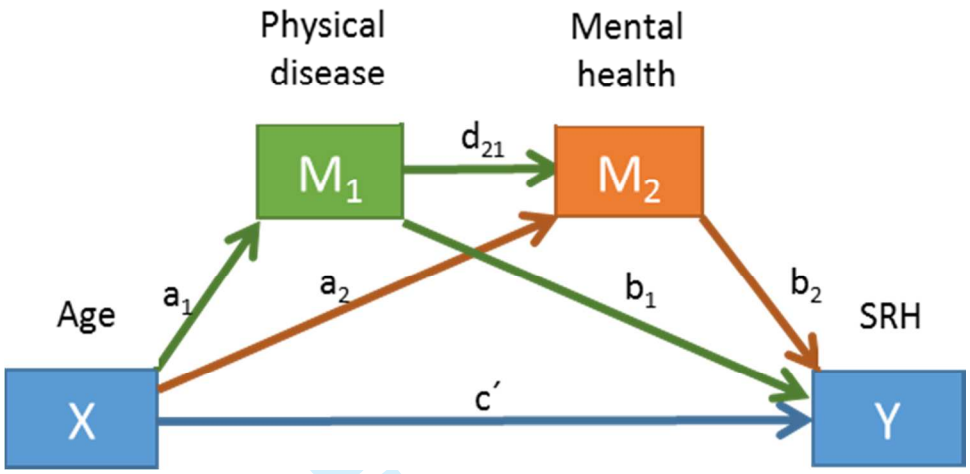
Figure 1. Conceptual and statistical diagram for the mediated effect of age on SRH through comorbid disease and mental health symptoms.

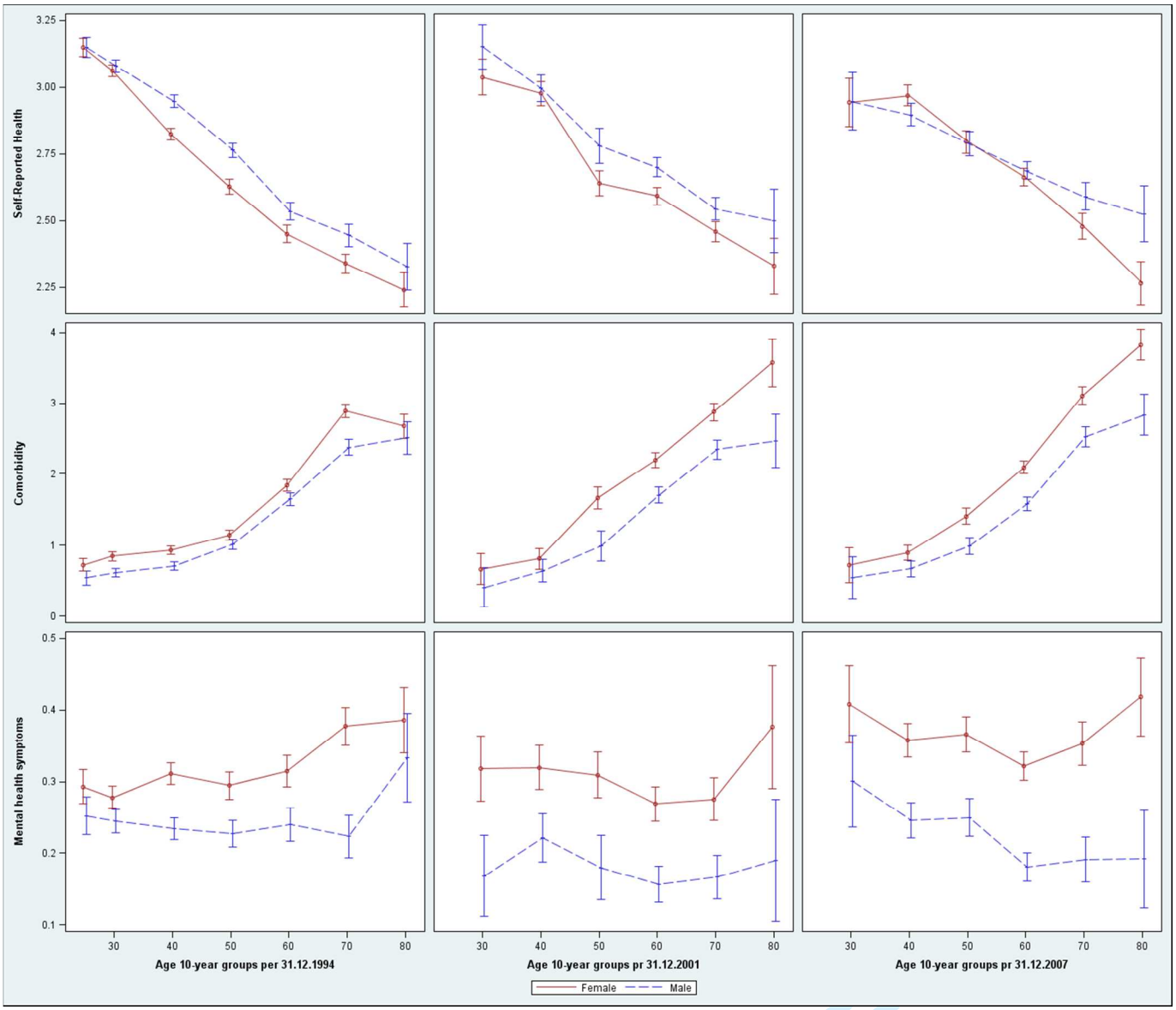


Indirect effect of X on Y through $M_i = a_i * b_i$

Indirect effect of X on Y through M_1 and M_2 in serial = $a_1 * d_{21} * b_2$

Direct effect of X on Y = c´

Figure 2. Profile plots for self-reported health for interaction effects between age and gender with 95% confidence intervals.



Self-reported health: Range from very poor (0) to very good (4) in TS 6, and poor (1) to very good (4) in TS 4 and 5.
Comorbid disease: Number of diseases grouped into a score with range 0-17 (Mean .97) in TS 4, range 0-17 (Mean 1.59) in TS 5; and range 0-19 (Mean 1.53) in TS 6.
Mental health symptoms: CONOR-MHI with range 1-4 (Mean 1.52) in TS 4, and HSCL-10 with range 1-4 in TS 5 and 6 (mean 1.25 in TS 5 and mean 1.29 in TS 6).
All differences p <0.001. Red lines = women, Blue dotted lines = men, CI 95% is SE*1.96

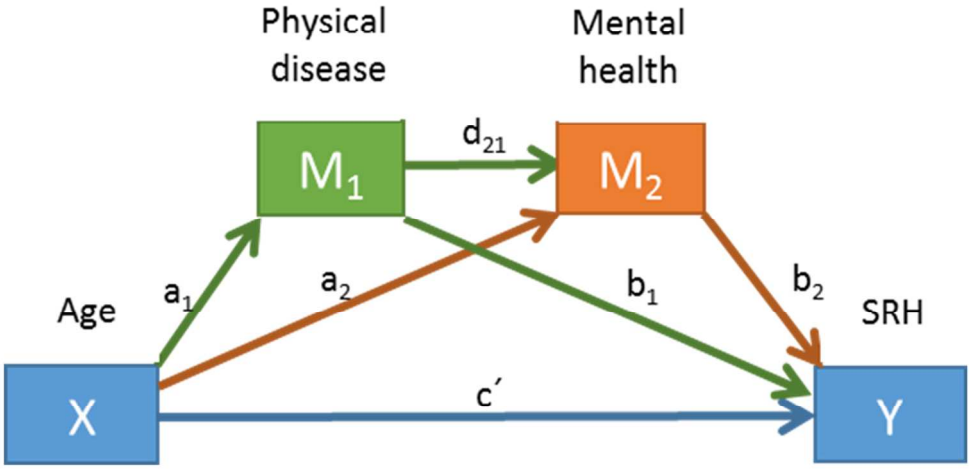
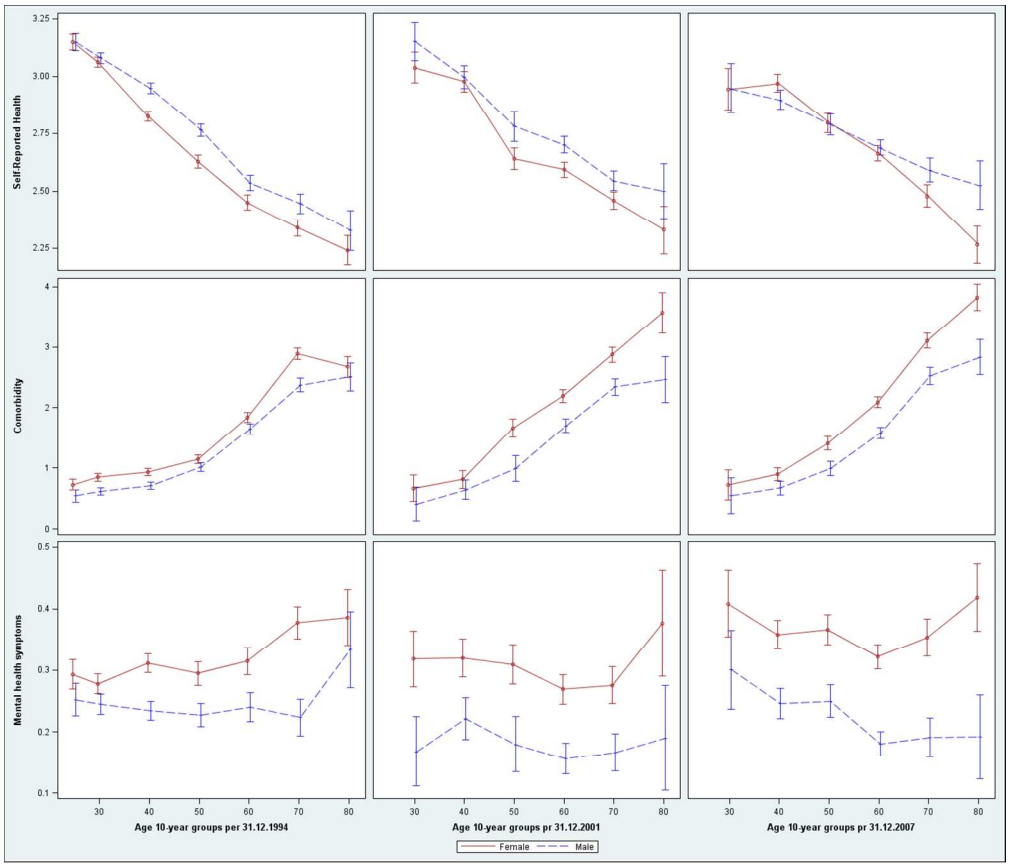


Figure 1 - conceptual and statistical diagram for the mediated effect of age on SRH through comorbid disease and mental health symptoms
(Insert Figure 1 here)
338x190mm (96 x 96 DPI)



Caption : Caption : Figure 2. Profile plots for Self-Reported Health for interaction effects between age and gender with 95% confidence intervals.
(Insert Figure 2 here)
355x304mm (100 x 100 DPI)

Appendix 1. Age standardized prevalence of comorbid conditions per 10 000 inhabitants with 95% confidence intervals in the Tromsø study cohorts

Comorbid conditions	Assigned weight [a]	Tromsø 4 (1994/5)			Tromsø 5 (2001)			Tromsø 6 (2007/8)		
		Rate	95% CI		Rate	95% CI		Rate	95% CI	
Chronic bronchitis	1	688	(652 -	724)	318	(279 -	358)	316	(286 -	346)
Migraine	1	1464	(1415 -	1513)	1386	(1255 -	1518)	1237	(1159 -	1315)
Gastric or ventricular ulcer	2	723	(682 -	764)	750	(671 -	829)	596	(552 -	640)
Asthma	2	677	(639 -	715)	754	(656 -	852)	836	(777 -	895)
Thyroid disease	2	370	(340 -	400)	547	(478 -	617)	695	(647 -	743)
Arthritis [b]	2	2799	(2594 -	3004)	2729	(2532 -	2926)	2073	(1916 -	2229)
Myocardial infarction	2	165	(144 -	187)	191	(163 -	219)	192	(169 -	215)
Cerebrovascular stroke	2	368	(336 -	400)	358	(318 -	398)	383	(353 -	414)
Diabetes (T1 or T2)	2	208	(184 -	231)	287	(237 -	336)	372	(336 -	407)
Osteoporosis	3	177	(154 -	200)	207	(179 -	234)	287	(260 -	315)
Angina	3	457	(431 -	483)	349	(318 -	380)	320	(293 -	347)

[a] Assigned weights for each condition the participant has according to the Health Impact Index that are used to measure comorbidity. The total equals the score, e.g. a patient with angina (3) and diabetes (2) will have a full contextual score of 3+2=5.
[b] Includes only subjects above 70 years of age.

Appendix 2. Regression coefficients with bias corrected standard errors for mediated effect of age on self-reported health. Confidence intervals and standard errors are based on 1000 bootstrap samples.

Consequent 1994

		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]	
Constant	i_{M1}	-0.733	-0.810	-0.656	i_{M2}	1.48526	1.467446	1.503073	i_y	4.421846	4.382292	4.461401
X (Age)	a_1	0.0390	0.037	0.041	a_2	0.000	-0.000315	0.0004202	c'	-0.014	-0.014472	-0.013333
M1 (Medical condition)		---	---	---	d_{12}	0.0297326	0.0262572	0.033208	b_1	-0.0704918	-0.074957	-0.066027
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.5594842	-0.57862	-0.540348
		R-squared = 0.1002				R-squared = 0.0169				R-squared = 0.2882		
		Wald $\chi2(1) = 1826.35$ p < .001				Wald $\chi2(2) = 309.30$, p<.001				Wald $\chi2(3) = 8907.28$, p < .001		

Consequent 2001

		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]	
Constant	i_{M1}	-1.520	-1.677	-1.363	i_{M2}	1.341679	1.304584	1.378773	i_y	4.217373	4.13278	4.301967
X (Age)	a_1	0.0551	0.052	0.058	a_2	-0.003	-0.003269	-0.0020216	c'	-0.010	-0.011255	-0.009182
M1 (Medical condition)		---	---	---	d_{12}	0.0378559	0.03291	0.0428018	b_1	-0.0772212	-0.084309	-0.070134
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.6020822	-0.644952	-0.559213
		R-squared = 0.1180				R-squared = 0.0451				R-squared = 0.2734		
		Wald $\chi2(1) = 1339.28$ p < .001				Wald $\chi2(2) = 239.84$, p<.001				Wald $\chi2(3) = 2295.51$, p < .001		

Consequent 2007/8

		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]	
Constant	i_{M1}	-2.020	-2.194	-1.847	i_{M2}	1.425522	1.388859	1.462185	i_y	5.278	5.197401	5.358518
X (Age)	a_1	0.0627	0.059	0.066	a_2	-0.0034595	-0.004095	-0.0028236	c'	-0.0075404	-0.00861	-0.006471
M1 (Medical condition)		---	---	---	d_{12}	0.0409442	0.0366294	0.0452591	b_1	-0.0843211	-0.091595	-0.077048
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.7412179	-0.77872	-0.703716
		R-squared = 0.1229				R-squared = 0.0471				R-squared = 0.2529		
		Wald $\chi2(1) = 1501.87$ p < .001				Wald $\chi2(2) = 358.15$ p<.001				Wald $\chi2(3) = 3165.11$, p < .001		

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract OK
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found OK
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported OK
Objectives	3	State specific objectives, including any prespecified hypotheses OK. See abstract and introduction
Methods		
Study design	4	Present key elements of study design early in the paper OK (consecutive cross sectional analyses within the Tromsø Study)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection See methods section.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants See under sample and design
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable See under measurements and appendix 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group See measurements
Bias	9	Describe any efforts to address potential sources of bias High attendance rate and we utilize all available data. Although there is 13% missing HSCL in Tromsø 5, multiple imputation show that missing data has little effect on our model (Average RVI = 0.0370).
Study size	10	Explain how the study size was arrived at See sample and design
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why We explain HII and HSCL under measurements, the analysis section explain the purpose and stages in the analysis.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding See under analysis
		(*b*) Describe any methods used to examine subgroups and interactions Interactions were checked in the multimediator analysis for gender and biological risk factors, but they did not affect the overall results.
		(*c*) Explain how missing data were addressed See added text under sample.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy

		N/A
		(e) Describe any sensitivity analyses Not shown due to word limit (samples are large enough to describe all clinical relevant differences)
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed See sample description
		(b) Give reasons for non-participation at each stage whole birth cohorts and random samples were invited.
		(c) Consider use of a flow diagram Not included
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders table 1 and results section 1
		(b) Indicate number of participants with missing data for each variable of interest Sample description
Outcome data	15*	Report numbers of outcome events or summary measures See table 2 and 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Unadjusted estimates (total effect) in table 2 and confounder-adjusted in table 3 and appendix 2
		(*b*) Report category boundaries when continuous variables were categorized N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses OK
Discussion		
Key results	18	Summarise key results with reference to study objectives ok
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ok
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ok
Generalisability	21	Discuss the generalisability (external validity) of the study results ok
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

No conflicts

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Ageing and mental health: changes in self-reported health due to physical illness and mental health status with consecutive cross sectional analyses

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Primary Subject Heading:	Mental health
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AGEING AND MENTAL HEALTH: CHANGES IN SELF-REPORTED HEALTH DUE TO PHYSICAL ILLNESS AND MENTAL HEALTH STATUS WITH CONSECUTIVE CROSS SECTIONAL ANALYSES

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ABSTRACT

Objectives: It is known that self-reported health (SRH) declines with increasing age, but also that comorbidity increases with age. We wished to examine how age transfers its effect to SRH through comorbid disease and mental illness and whether these processes remained stable from 1994 until 2008. The hypothesis is that ageing and/or the increased age-related burden of pathology explains the declining SRH.

Setting: The Tromsø Study (TS) is a cohort study utilizing a survey approach with repeated physical examinations. It was conducted in the municipality of Tromsø, Norway, from 1974 to 2008.

Participants: A total of 21199 women and 19229 men participated.

Primary and secondary outcome measures: SRH is the outcome of interest. We calculated and compared the effect sizes of age, comorbidity and mental health symptoms utilizing multi-mediator analysis based on OLS regression.

Results: Ageing had a negative impact on SRH, but the total effect of age decreased from 1994 to 2007. We assessed the direct effect of age, and then the proportion of indirect age related effects through physical illness and mental health symptoms on the total effect. The direct effect of age represented 79.3% of the total effect in 1994 and decreased to 58.8% in 2007. Physical illness emerged as an increasingly important factor and increased its influence from 15.7% to 41.2% of the total effect. Age alone had a protective effect on mental health symptoms and this increased (2.5% to 17.3%), but we found a stronger association between mental health symptoms and physical disease in the later waves of the study (increasing from 3.7% to 14.8%).

Conclusions: The results suggest that the effect on SRH of mental health symptoms caused by physical illness is an increasing public health problem. Treatment and care for specific medical

conditions must therefore focus more strongly on how these conditions affect the patient's mental health and address these concerns accordingly.

Keywords: The Tromsø study, epidemiology, mental health, comorbid disease, self-reported health, ageing.

Strengths and limitations of this study:

- The sample comprises large, representative samples of a general population with repeated measures at approximately seven-year intervals.
- Multi-mediator analysis allows for the interpretation of the joint effect of age, comorbid disease and mental health on self-reported health.
- We utilized the repeated measures as separate cross sectional data in the analysis.
- The first three panels (1974-1986) did not include any adequate measurement of mental health symptoms and were excluded, but the CONOR-MHI (1994) was validated against the Hopkins Symptom Checklist (HSCL) and showed good agreement.

INTRODUCTION

Self-reported health (SRH) is a subjective assessment of current health status as seen by the patient or participant. It is well known that a whole range of biological, psychological and socio-economic factors affect SRH, but also that these factors interact.[1-5] The research literature suggests that SRH is

produced in a cognitive process that is inherently subjective and contextual, but also that SRH predicts mortality and other health outcomes; this shows that the basis of self-rated health lies in the biological and physiological state of the individual organism.[6] Well-known crucial biological factors that independently affect SRH are specific medical conditions (e.g. cardiovascular diseases, diabetes and asthma) and health risk factors (e.g. resting heart rate, blood pressure, cholesterol, BMI, and endocrine measures). Although the effect of SRH attenuates when such variables are controlled for, SRH still remains as an independent variable for all-cause death and other future health outcomes.[7-11] Mental health symptoms affect SRH, but mental health is also affected by physical disease. The literature suggests that severity of mental health symptoms correlates with many specific medical conditions, and consequently with impaired well-being. Comorbid strain increases with increasing age, and older people are particularly at risk of experiencing anxiety and depression.[12-17]

To summarize, it is well-documented that SRH declines with increasing age but whether it is ageing alone or the increased age-related burden of pathology that explains this association is still unanswered. The prevalence of coexisting chronic conditions is rising as life expectancy increases in contemporary Western society.[18] The age-specific decline could mean that the increasing level of pathology due to age explains this specific decline of SRH and not ageing by itself.

There are to our knowledge no studies that describe the combined effect of ageing, comorbid physical disease and mental health symptoms on general perceived health status. Moreover, since medical treatment has improved over the last three decades, leading to increased life expectancy, it seems timely to ask whether people's experiences of ageing, comorbid disease and mental health problems remain the same. We wished to examine how age transfers its effect on SRH through comorbid physical disease and mental health symptoms. A further aim was to explore how mental health symptoms are affected by physical disease and whether these processes remained stable from 1986 until 2008.

METHOD

Sample and design

The Tromsø Study (TS) was a cohort study which provided data allowing us to estimate the impact of a broad range of factors on a general population, utilizing surveys and physical examinations in a large representative sample.[19] TS consisted of six surveys conducted in Tromsø in Northern Norway from 1974 to 2008. We utilized consecutive cross sectional analyses within the Tromsø Study. The study population was recruited from all inhabitants in specific age groups. The aim was to include large, representative samples of the Tromsø population, with the invitation of whole birth cohorts and random samples. The attendance rate was high (66-75%). A total of 21199 women and 19229 men gave informed signed consent and attended up to six separate health examinations. Tromsø 1 was a heart study conducted in 1974 and included only men aged 20-49. Tromsø 2 followed up the first study in 1979-80 but included both men (aged 20-54) and women (aged 20-49). Tromsø 3 was executed in 1986-87 and included men and women in the 20-56 age range, and a 10% random selection of persons aged 12-19. We excluded Tromsø 1-3. SRH was introduced during the 1980s; Tromsø 1and 2 thus lack SRH and Tromsø 3 did not include any adequate measurement of mental health symptoms. Our sample starts with Tromsø 4 in 1994. Tromsø 4 is the largest wave and participants were followed up in 2001 and 2007/8. We excluded those with missing data (n=736 in TS4, n=1132 in TS5, n=767 in TS6). The final analysis therefore comprised 12408 men and 13579 women from TS4, 3108 men and 3746 women from TS5, and 5769 men and 6338 women from TS6. The Norwegian Data Protection Authority and the Regional Committees for Medical and Health Research Ethics North Norway approved the Tromsø Study.

Measurements

The participants completed a self-administrated questionnaire with questions on a broad range of diseases and symptoms, health behaviour, social conditions, education, financial situation and level of physical activity. *Self-Reported Health (SRH):* The independent variable SRH was reported by answering the question "What is your current state of health?" with answers ranging from very bad (0) to very good (4) in Tromsø 6, and from poor (1) to very good (4) in Tromsø 4 and 5. *Specific medical conditions:* We selected 13 symptomatic medical conditions reported in all panels. These were psoriasis, food allergies, chronic bronchitis, migraine, ulcer, asthma, thyroid disease, arthritis, myocardial infarction, cerebrovascular stroke, diabetes, osteoporosis, and angina. The conditions were self-reported by answering questions such as "Do you have or have you had....?" We utilized the Health Impact Index (HII) to measure the comorbid conditions. Diseases have a varied impact on SRH. HII classifies patients with comorbid disease according to the impact that each condition has on SRH by assigning a weight for each condition. HII equals the total score of each condition of the participant. HII thus considers both the severity and joint effects of the conditions.[4] The range was 0-18 in TS4, 0-17 in TS5 and 0-22 in TS 6. Appendix 1 shows the conditions included with their weights and prevalence in the different waves.

Mental health symptoms were based on well validated self-report symptom inventory comprising questions representative of the symptom configurations of anxiety and depression commonly observed among outpatients. It includes questions such as "Have you experienced sudden fear without apparent reason", "…felt tense or upset", "…easily blamed yourself", "…felt depressed or sad", "…felt useless or worthless", "…felt that everything is a struggle" or "…felt hopelessness". Each answer is scored from 1 to 4. The measurement is the average score. The range was therefore 1-4 in all waves. The mental health index (CONOR-MHI) used at T4 have been compared with the Hopkins Symptom Checklist (HSCL) with reasonably good agreement. In the following surveys T5-6, the Hopkins

Symptom Checklist (HSCL) was used. A cut-off level of 2.15 for significant symptoms is equivalent to the 1.85 level in HSCL-10.[20, 21]

Analysis

The purpose of the descriptive statistics was to define the distribution of SRH, comorbid disease and mental health across samples, age groups, and gender. We used cross tabulation and two-way ANOVA to describe the characteristics of the sample. *Multi-mediator analysis* was used for the analysis of the conditional nature of the mechanism by which age transmits its effect on SRH. The advantage of this method is that it allows for the interpretation of multiple confounders that may function as either mediators or moderators and interprets their joint effect on the statistical model derived from the theoretical model.[22, 23] The analytical goal of the multi-mediation analysis was to determine how age transfers its effect to SRH directly and through physical disease and mental illness. The first step was the conceptual model, which we based on the idea that age represents the timeline of life in which events like disease occur and physical condition changes. Previous analysis, tracking individual subjects, confirms that SRH decreases with increasing age and whenever levels of pathology increase. This implies that age might influence SRH either directly or indirectly through pathology as life events. The second step was to translate the conceptual model into a statistical model. Figure 1 shows the conceptual model and its translation into a statistical model.[24] The statistical model includes SRH as outcome (Y), age as the main variable (X) with medical condition (M_1) and mental health symptoms (M_2) as mediators. Our statistical model includes three indirect effect lines (Ind 1-3).

- Ind 1: Age→HII→SRH (a_1*b_1)
- Ind 2: Age→HII→HSCL→SRH (a_1*d_{21}*b_2)
- Ind 3: Age→HSCL→SRH (a_2*b_2)

We used multiple regression to assess the two mediators (M_1=Medical conditions and M_2= Mental health) and the reaction (Y=SRH). The regression coefficients, 95% confidence intervals, and model summary information for the mediated effect of age on self-reported health have been published as supplementary material (Appendix 2).

(Insert Figure 1 here)

RESULTS

Characteristics and total effect of age

Table 1 shows the characteristics of the four samples indicating increasing comorbidity with a shift in 2001 (T5) when the comorbid levels decreased with a corresponding increase in SRH. Figure 2 shows profile plots for SRH, comorbidity and ratio of persons with sub-threshold and significant mental health symptoms across age and gender. Testing for gender and age differences with two-way ANOVA showed that all mean differences were significant ($p<.0001$) for SRH. Here, SRH declined significantly with increasing age with a corresponding increase in comorbidity at all three survey points. Although the gender differences were statistically significant for all three factors, the gender difference in SRH was less than a ten-year age difference in SRH in all surveys. For comorbidity, the gender difference was as large as a ten-year age difference for the two intermediate survey points, but less so at the first and last where the gender difference was small. For comorbidity, the most striking finding was the increase by age across all surveys, especially for women, who had an increasing burden

of disease as they got older. For mental health symptoms, the greater burden for women was most striking.

Table 1. Distribution of SRH, physical condition and demographics, specific medical conditions, mental health symptoms and social context by gender in Tromsø 4-6 (1994-2008)

	Tromsø 4		Tromsø 5		Tromsø 6	
Self-Rated Health (Mean/SD)	2.82	(0.70)	2.7	(0.67)	2.74	(0.77)
Age (Mean/SD)	48.1	(14.8)	60.1	(13.8)	58.7	(12.4)
Health impact index (Mean/SD)	0.95	(1.66)	1.72	(2.18)	1.66	(2.21)
Mental health symptoms (Mean/SD)	1.25	(0.36)	1.29	(0.38)	1.52	(0.41)

(Insert figure 2 here)

The total effect of age

We utilized an OLS regression model to determine the total effect of age on SRH. Table 2 shows the linear model of the total effect of age on SRH. We see that age had a negative effect on SRH in all samples, but also that the total effect of age attenuated from 1994 to 2008 in parallel with increasing life expectancy in the region. Each year of age represented -0.0175 (CI: -0.018, -0.017) deterioration of SRH in T4 but the effect dropped to -0.013 (CI: -0.014, -0.012) in T6.

Table 2. Linear model of the total effect of age on Self-Reported Health with 95% confidence intervals. Confidence intervals and standard errors are based on 1000 bootstrap samples.

	Tromsø 4			Tromsø 5			Tromsø 6		
	Coeff.	[95% CI)		Coeff.	[95% CI)		Coeff.	[95% CI)	
Age	-0.0175	-0.0181	-0.0170	-0.0146	-0.0157	-0.0136	-0.0128	-0.0139	-0.0117
Constant	3.6584	3.6311	3.6856	3.5742	3.5111	3.6372	3.4840	3.4179	3.5500
Note:	$F(1, 25195) = 4039.67$. $P< 0.0001$. $R^2 = 0.1382$			$F(1, 7764) = 783.57$. $P<0.0001$. $R^2 = 0.0917$			$F(1, 11962) = 519.36$. $P< 0.0001$. $R^2 = 0.0416$		

The indirect effect of pathology

The M_1 models in Appendix 2 show that higher comorbidity was associated with increasing age in all waves (Coeff.=.050 in T4; .059 in T5; .050 in T6). The M_2 models show a significant effect for age on mental health symptoms (Coeff.= -0.0002 in T4; -0.0025 in T5; -0.0029 in T6), although medical conditions when they occurred affected mental health symptoms more than age (.030 in T4; .032 in T5; .041 in T6). All effect lines in the statistical model were estimated by series of OLS regression models (see Appendix 2 in the supplementary material). Table 3 shows the indirect and direct effects of age on SHR. We calculated these from the coefficients in Appendix 2 according to our statistical model. Adding gender as a moderator on each effect line did not change the overall results.

Table 3. Direct and indirect effect size with 95% bias corrected confidence intervals in parentheses, standard errors and ratio of indirect to direct effect of age on self-reported health. Confidence intervals and standard errors are based on 1000 bootstrap samples.

	Tromsø 4			**Tromsø 5**			**Tromsø 6**		
	Effect (95% CI)			Effect (95% CI)			Effect (95% CI)		
Total effect of age on SRH:	**-0.0175**	-0.0181	-0.0170	**-0.0146**	-0.0157	-0.0136	**-0.0128**	-0.0139	-0.0117
Indirect effect of age on SRH:									
Total:	**-0.0034**	-0.0032	-0.0037	**-0.0039**	-0.0034	-0.0043	**-0.0046**	-0.0040	-0.0052
Age→HII→SRH:	**-0.0027**	-0.0028	-0.0027	**-0.0043**	-0.0044	-0.0041	**-0.0053**	-0.0054	-0.0051
Age→HII→HSCL→SRH:	**-0.0006**	-0.0006	-0.0007	**-0.0013**	-0.0011	-0.0014	**-0.0019**	-0.0017	-0.0021
Age→HSCL→SRH:	**0.000***	0.0002	-0.0002	**0.0016**	0.0021	0.0011	**0.0026**	0.0032	0.0020
Ratio of indirect to total effect of age on SRH:									
Total:	**0.195**	0.176	0.215	**0.267**	0.217	0.318	**0.360**	0.284	0.442
Age→HII→SRH:	**0.157**	0.154	0.158	**0.290**	0.281	0.299	**0.412**	0.391	0.433
Age→HII→HSCL→SRH:	**0.037**	0.031	0.043	**0.086**	0.071	0.102	**0.148**	0.122	0.179
Age→HSCL→SRH:	**0.002***	-0.010	0.013	**-0.109**	-0.135	-0.083	**-0.200**	-0.229	-0.170

Note: Indirect effect of X on Y through Mi only = ai * bi, Indirect effect of X on Y through M1 and M2 in serial = a1 * d21 * b2, Direct effect of X on Y = c', The ratio of indirect effect to direct effect = Mi/c´(Figure 1 - statistical diagram). Note 2: *= Confidence intervals include zero.

We found that age had both a direct and indirect effect on SRH. The direct effect (c´) of age attenuated from 1994 to 2008 (T4: c' =-0.013, T5: c' = -0.011, T6: c' = -0.008). This suggests not only

that age affected SRH independently of pathology even when controlling for the mediators, but also that age itself had a lower impact on SRH at the latest measuring point.

We found that age had an increasing negative indirect effect through comorbid diseases (T4: -0.0034; T5: -0.0035; T6: -0.0042). Since the total effect attenuated in the same period, this implied that the ratio of total to indirect effect of comorbid disease increased correspondingly more. It was 0.192 in 1994, 0.236 in 2001 and 0.330 in 2007/8. This trend implied that physical disease was an increasingly important factor relative to age itself to explain why SRH declines with increasing age.

The second indirect effect (Age→HII→HSCL→SRH) included mental health symptoms associated with having a disease. We found a negative effect on SRH T4 of -0.0006, T5 of -0.0013 and T6 of -0.0019. This suggests that having a physical disease was associated with higher levels of mental health symptoms, which in turn affected SRH. The ratio of total to indirect effect of comorbid disease was -0.037 in T4, -0.086 in T5 and -0.148 in T6. Thus, we see a consistent increase in the relative size of the second indirect effect from 1994 to 2007/8. This implied that the relative significance of mental health issues connected to physical disease increased during this period, and at 14.8% of the total effect, it is also clinically significant.

The third indirect effect line (Age→HSCL→SRH) revealed that SRH increased with increasing age, which implies that mental health symptoms are associated with increasing age when controlled for physical disease. The ratio of effect size increased during this period from 0.002 in T4 to -0.0109 in T5 and -0.200 in T6. This implied that when we disregard physical illness and mental health problems associated with physical illness, increasing age had a beneficial effect on SRH.

DISCUSSION

Ageing affected self-reported health (SRH) directly and also indirectly through increased levels of pathology. We observed a change in how ageing and physical disease influenced SRH between the different waves. The direct effect of ageing (c') represented 79.3% of the total effect in 1994, 69.8% in 2001, and 58.8% in 2007/8. This means that ageing is still the most important factor for SRH, but that ageing itself became relatively less important between the waves. Meanwhile, physical disease became an increasingly important factor for SRH. As shown in Table 3, comorbid conditions (HII) represented 15.7% of the total effect in 1994, 26.7% in 2001, and 41.2% in the last wave in 2007/8. Furthermore, ageing itself had a protective effect on mental health symptoms which increased (2.0% to 20.0% of the total effect). We found a stronger association between mental health symptoms and physical disease in the later waves (increasing from 3.7% to 14.8%). Mental health symptoms related to physical disease consequently led to lower SRH levels in the later parts of the study.

Physical disease is known to be related to mental health symptoms of anxiety and depression, which the HSCL-10 scale is especially sensitive to measure in a general population.[15] Epidemiological data suggest that severity of mental health symptoms correlates with disease, e.g. one third of stroke survivors develop depression [12] and one quarter anxiety disorders.[13] Cardiovascular diseases have shown discrete effects for panic disorder and specific phobia.[14, 15] Older people with illnesses such as coronary heart disease, arthritis, and chronic lung disease show both increased levels of depressed mood and impaired well-being.[16] Cumulative stress exposure across different stress domains contributes to depressive symptoms in cancer survivors.[17] Moreover, pessimism, negative cancer-related rumination, and physical symptom distress predicted both anxiety and depression trajectories.

However, our findings indicate that physical disease in recent decades has become more strongly associated with mental health symptoms, i.e. the indirect effect on mental health symptoms via

physical disease has increased over time. Accordingly, it seems plausible that physical diseases in terms of SRH affect us more than before, but also that physical disease has a greater impact on our reaction towards illness than before. So, how can we explain these findings? Why does physical disease trigger symptoms of anxiety and depression more often than before?

One possible explanation may be found in social changes in Norway and the Norwegian healthcare system. Although we today have curative and palliative treatment of many more physical disorders, and more individuals have access to treatment, there is also an increased expectation of "active ageing" and healthy living.[25, 26] This expectation is realistic, as the incidence of especially cardiovascular diseases has been rapidly declining for several decades, but is contrasted by a decreasing case fatality, leaving more of those who still get cancer, coronary heart attacks and stroke with lasting disability as more people survive.[27]

SRH can reflect the states of the human body and mind. People base their health assessments on different types of information and contextual frameworks.[6] It is plausible that people who expect to age actively become unhappy or worried when encountering limitations and disease. It may also be argued that people tend to respond negatively to questions on their health or limitations when comparing their situation with others at similar age. Bodily sensations that are directly available to the individual are another source of information.[6] Accordingly, it seems plausible that people compare current body status with the situation before the disease occurred, and experience fear of relapse or having another disease. We cannot answer this assumption based on three cross-sectional analyses; however, it is a hypothesis that could be answered by tracking individuals in the Tromsø study cohort.

Furthermore, current healthcare services are organized to place greater emphasis on efficiency than on care, and society has a faster pace of life so that older people live more often alone and isolated than a few decades ago. From an evolutionary perspective, symptoms of anxiety and depression are understood as normal reactions to life-threatening and uncontrollable situations. For example, fear is an

obvious adaptive function as it stimulates the "fight-or-flight" response when the individual is exposed to a threat or dangerous situation; unless the individual can escape, it will hide or "freeze" the situation.[28] Furthermore, Gilbert describes anxiety disorders as a maladaptive expression or phenotype of the original functional fear system where the acute stress response is triggered in an inappropriate manner.[29] Similarly, Nettle proposes that depression may represent a maladaptive expression of an original functional control system for positive affect, i.e., a functional downregulation of positive affect in certain situations and contexts.[30] Gilbert describes such a downregulation of positive affect as a defensive reaction, a similar fight-or-flight response, in situations where the individual experiences loss of control over aversive events or over significant resources including the social environment.[29] An increased incidence of comorbid physical disorders with consequent reduced access to social participation can thus be a plausible explanation of an increase in mental symptoms related to physical disorders.

Interestingly, we found that age by itself was protective of mental health symptoms when controlled for the mental health symptoms associated with physical illness. Several studies focus on how physical disease is associated with increased risk of mental health symptoms. In our study, this mechanism represented 4% of the total effect in 1986, 5% in 1994, 6% in 2001 and 12% in 2008. Our findings concur with studies on patient populations showing that mental health is an important aspect of impairment of SRH when physical illness occurs.

Strengths and limitations of the method

HII includes 13 symptomatic medical conditions, but does not include risk factors such as hypertension or dyslipidemia. These could be included as mediators on the age->HII->SRH effect line, but this did not change the overall findings of the model. The Tromsø study includes cancer but it is self-reported and does not distinguish between those with an active illness and those who have had

cancer. That was the most likely explanation for why it did not add to the model[4] and it was therefore not included.

Although measured on an ordinal scale, the underlying phenomenon of SRH is continuous, and the scales represent similar logical increments. Furthermore, the distribution of SRH, apart from being staggered, resembled the shape of a normal distribution. Hence, an OLS regression model could be used for the analysis of independent associations in the multivariable model.[22] Adding gender as a moderator on each effect line did not change the overall results. Mental health symptoms were measured with different instruments, which may have affected our findings. T5 and T6 used the Hopkins Symptom Check List (HSCL-10), which is a self-reported symptom inventory comprising ten items representative of the symptom configurations of anxiety and depression commonly observed among outpatients.[20] T4 used the CONOR Mental Health Index (MHI). This was based on seven questions concerning different symptom configurations of anxiety and depression. It was partly derived from HSCL-10 and the General Health Questionnaire (GHQ). Fortunately, Tromsø 4 is included in the CONOR database that also included HSCL-10. The index has therefore been compared with HSCL-10 with reasonably good agreement. It has been concluded that the scales can be used in epidemiological studies. For comparisons, it is recommended to use the cut-off level of 2.15 for significant symptoms as equivalent to the 1.85 level in HSCL-10.[21, 31]

CONCLUSION

As medicine advances and life expectancy increases, we have higher expectations for the healthcare system and to remain healthy even in old age. The results suggest that the effect on SRH of mental health symptoms caused by physical illness is an increasing public health problem. It seems that our

resilience to diseases is decreasing. Therefore, treatment and care for specific medical conditions must focus more strongly on how these conditions affect the patient's mental health and address these concerns accordingly.

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CONTRIBUTOR STATEMENT

Profs Lorem, Schirmer, Wang and Emaus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lorem, Schirmer, and Emaus. Acquisition, analysis or interpretation of data: Lorem, Schirmer, Wang and Emaus. Statistical analysis: Lorem. Drafting of the manuscript: Lorem. Critical revision of the manuscript for important intellectual content: Lorem, Schirmer, Wang and Emaus. Administrative, technical or material support: The Tromsø Study of UiT The Arctic University of Norway provided the data. Conflict of interest disclosures: The authors declare no conflicts of interests. Funding/Support: UiT The Arctic University of Norway funded the study. Role of the funder/sponsor: The study sponsor had no role in the design and implementation of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication. Obtained funding: Emaus.

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DATA SHARING STATEMENT

We received the data from the Tromsø study. The data contain sensitive health information about the participants. Data cannot be made publicly available without compromising participant confidentiality and privacy. Directives from the Research Ethical Committee and the Norwegian Data Protection Authority thus prohibit us from making the minimal data set publicly available. Data is available from the Tromsø study for researchers who meet the criteria for access to confidential data (https://en.uit.no/prosjekter/prosjekt?p_document_id=80172). Furthermore, all variables are described in the NESSTAR database: http://tromsoundersokelsen.uit.no/webview/

COMPETING INTERESTS

Competing interests: None.

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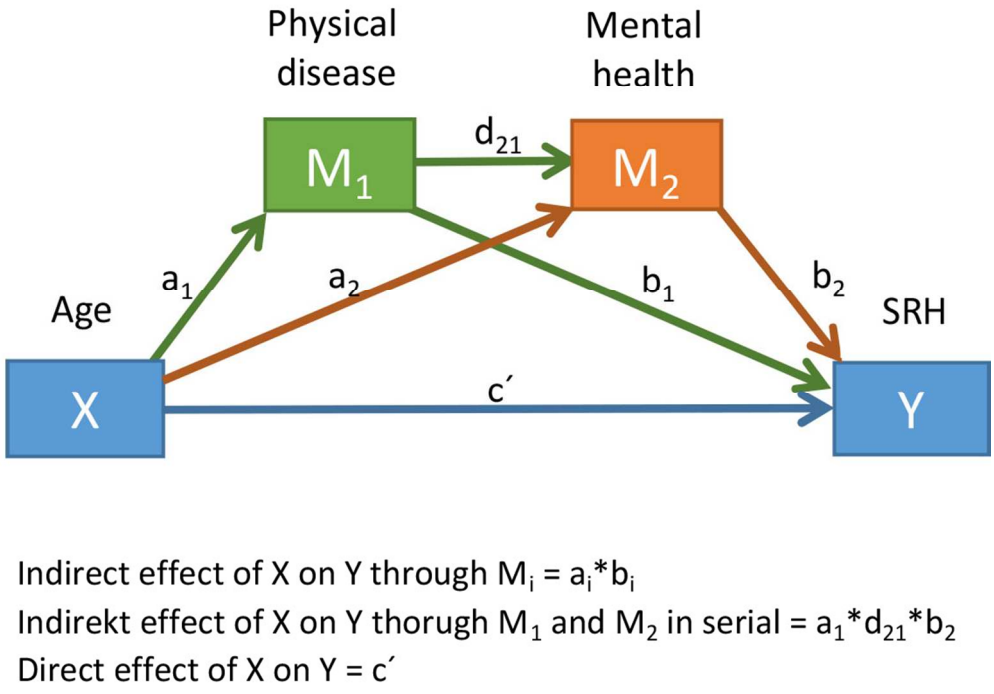
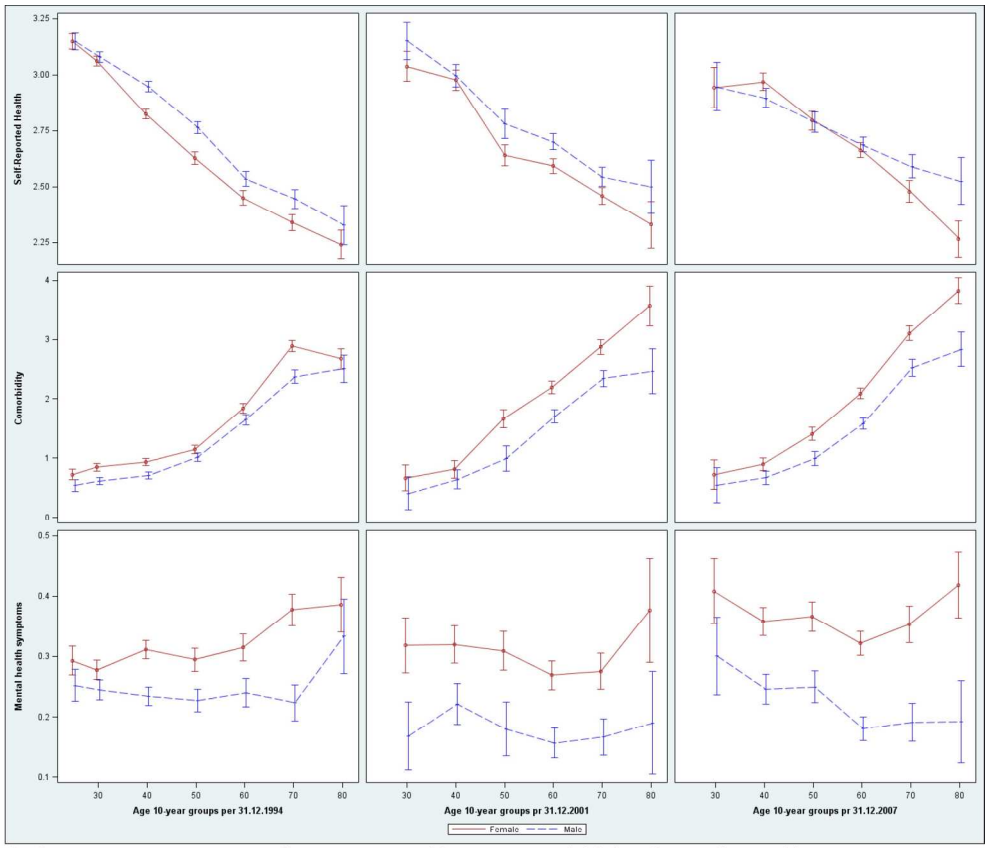


Figure 1. Conceptual and statistical diagram for the mediated effect of age on SRH through comorbid disease and mental health symptoms.
(Insert Figure 1 here)
97x69mm (300 x 300 DPI)



Self-reported health: Range from very poor (0) to very good (4) in TS 6, and poor (1) to very good (4) in TS 4 and 5.
Comorbid disease: Number of diseases grouped into a score with range 0-17 (Mean .97) in TS 4, range 0-17 (Mean 1.59) in TS 5; and range 0-19 (Mean 1.53) in TS 6.
Mental health symptoms: CONOR-MHI with range 1-4 (Mean 1.52) in TS 4, and HSCL-10 with range 1-4 in TS 5 and 6 (mean 1.25 in TS 5 and mean 1.29 in TS 6).
All differences p <0.001. Red lines = women, Blue dotted lines = men, CI 95% is SE*1.96

Figure 2. Profile plots for self-reported health for interaction effects between age and gender with 95% confidence intervals.
(insert figure 2 here)
184x189mm (300 x 300 DPI)

Appendix 1. Age standardized prevalence of comorbid conditions per 10 000 inhabitants with 95% confidence intervals in the Tromsø study cohorts

Comorbid conditions	Assigned weight [a]	Tromsø 4 (1994/5)			Tromsø 5 (2001)			Tromsø 6 (2007/8)		
		Rate	95% CI		Rate	95% CI		Rate	95% CI	
Chronic bronchitis	1	688	(652 -	724)	318	(279 -	358)	316	(286 -	346)
Migraine	1	1464	(1415 -	1513)	1386	(1255 -	1518)	1237	(1159 -	1315)
Gastric or ventricular ulcer	2	723	(682 -	764)	750	(671 -	829)	596	(552 -	640)
Asthma	2	677	(639 -	715)	754	(656 -	852)	836	(777 -	895)
Thyroid disease	2	370	(340 -	400)	547	(478 -	617)	695	(647 -	743)
Arthritis [b]	2	2799	(2594 -	3004)	2729	(2532 -	2926)	2073	(1916 -	2229)
Myocardial infarction	2	165	(144 -	187)	191	(163 -	219)	192	(169 -	215)
Cerebrovascular stroke	2	368	(336 -	400)	358	(318 -	398)	383	(353 -	414)
Diabetes (T1 or T2)	2	208	(184 -	231)	287	(237 -	336)	372	(336 -	407)
Osteoporosis	3	177	(154 -	200)	207	(179 -	234)	287	(260 -	315)
Angina	3	457	(431 -	483)	349	(318 -	380)	320	(293 -	347)

[a] Assigned weights for each condition the participant has according to the Health Impact Index that are used to measure comorbidity. The total equals the score, e.g. a patient with angina (3) and diabetes (2) will have a full contextual score of 3+2=5.

[b] Includes only subjects above 70 years of age.

Appendix 2. Regression coefficients with bias corrected standard errors for mediated effect of age on self-reported health. Confidence intervals and standard errors are based on 1000 bootstrap samples.

Consequent 1994												
		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]	
Constant	i_{M1}	-0.733	-0.810	-0.656	i_{M2}	1.48526	1.467446	1.503073	i_y	4.421846	4.382292	4.461401
X (Age)	a_1	0.0390	0.037	0.041	a_2	0.000	-0.000315	0.0004202	c'	-0.014	-0.014472	-0.013333
M1 (Medical condition)		---	---	---	d_{12}	0.0297326	0.0262572	0.033208	b_1	-0.0707918	-0.074957	-0.066027
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.5594842	-0.57862	-0.540348
		R-squared = 0.1002				R-squared = 0.0169				R-squared = 0.2882		
		Wald $\chi2(1) = 1826.35$ p < .001				Wald $\chi2(2) = 309.30$, p<.001				Wald $\chi2(3) = 8907.28$, p < .001		
Consequent 2001												
		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]	
Constant	i_{M1}	-1.520	-1.677	-1.363	i_{M2}	1.341679	1.304584	1.378773	i_y	4.217373	4.13278	4.301967
X (Age)	a_1	0.0551	0.052	0.058	a_2	-0.003	-0.003269	-0.0020216	c'	-0.010	-0.011255	-0.009182
M1 (Medical condition)		---	---	---	d_{12}	0.0378559	0.03291	0.0428018	b_1	-0.0773212	-0.084309	-0.070134
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.6020822	-0.644952	-0.559213
		R-squared = 0.1180				R-squared = 0.0451				R-squared = 0.2734		
		Wald $\chi2(1) = 1339.28$ p < .001				Wald $\chi2(2) = 239.84$, p<.001				Wald $\chi2(3) = 2295.51$, p < .001		
Consequent 2007/8												
		M1 (Medical conditions)				*M2 (Mental health)*				*REACTION (Self-reported health)*		
Antecedent		Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]			Coeff.	[95% Conf. Interval]	
Constant	i_{M1}	-2.020	-2.194	-1.847	i_{M2}	1.425522	1.388859	1.462185	i_y	5.278	5.197401	5.358518
X (Age)	a_1	0.0627	0.059	0.066	a_2	-0.0034595	-0.004095	-0.0028236	c'	-0.0075404	-0.00861	-0.006471
M1 (Medical condition)		---	---	---	d_{12}	0.0409442	0.0366294	0.0452591	b_1	-0.0846211	-0.091595	-0.077048
M2 (Mental health)		---	---	---		---	---	---	b_2	-0.7414179	-0.77872	-0.703716
		R-squared = 0.1229				R-squared = 0.0471				R-squared = 0.2529		
		Wald $\chi2(1) = 1501.87$ p < .001				Wald $\chi2(2) = 358.15$ p<.001				Wald $\chi2(3) = 3165.11$, p < .001		

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract OK
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found OK
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported OK
Objectives	3	State specific objectives, including any prespecified hypotheses OK. See abstract and introduction
Methods		
Study design	4	Present key elements of study design early in the paper OK (consecutive cross sectional analyses within the Tromsø Study)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection See methods section.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants See under sample and design
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable See under measurements and appendix 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group See measurements
Bias	9	Describe any efforts to address potential sources of bias High attendance rate and we utilize all available data. Although there is 13% missing HSCL in Tromsø 5, multiple imputation show that missing data has little effect on our model (Average RVI = 0.0370).
Study size	10	Explain how the study size was arrived at See sample and design
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why We explain HII and HSCL under measurements, the analysis section explain the purpose and stages in the analysis.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding See under analysis
		(*b*) Describe any methods used to examine subgroups and interactions Interactions were checked in the multimediator analysis for gender and biological risk factors, but they did not affect the overall results.
		(*c*) Explain how missing data were addressed See added text under sample.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy

		N/A
		(e) Describe any sensitivity analyses Not shown due to word limit (samples are large enough to describe all clinical relevant differences)
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed See sample description
		(b) Give reasons for non-participation at each stage whole birth cohorts and random samples were invited.
		(c) Consider use of a flow diagram Not included
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders table 1 and results section 1
		(b) Indicate number of participants with missing data for each variable of interest Sample description
Outcome data	15*	Report numbers of outcome events or summary measures See table 2 and 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Unadjusted estimates (total effect) in table 2 and confounder-adjusted in table 3 and appendix 2
		(*b*) Report category boundaries when continuous variables were categorized N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses OK
Discussion		
Key results	18	Summarise key results with reference to study objectives ok
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ok
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ok
Generalisability	21	Discuss the generalisability (external validity) of the study results ok
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

No conflicts

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.