Comparing the impact of personal and parental risk factors, and parental lifespan on all cause mortality and cardiovascular disease: findings from the Midspan Family cohort study

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Abstract

Background

We aimed to identify which personal and parental factors best explained all cause mortality and cardiovascular disease (CVD).

Methods

In 1996, data were collected on 2338 adult offspring of the participants in the 1972-1976 Renfrew and Paisley prospective cohort study. Recorded risk factors were assigned to five groups: mid-life biological and behavioural (BB), mid-life socioeconomic (SE), parental BB, early-life SE and parental lifespan. Participants were followed up for mortality and hospital admissions to the end of 2011. Cox proportional hazards models were used to analyse how well each group explained all cause mortality or CVD. Akaike's Information Criterion (AIC), a measure of goodness-of-fit, identified the most important groups.

Results

For all cause mortality (1997 participants with complete data, 111 deaths), decreases in AIC from the null model (adjusting for age and sex), to models including mid-life BB, mid-life SE, parental BB, early-life SE and parental lifespan were 55.8, 21.6, 10.3, 7.3 and 5.9 respectively. For the CVD models (1736 participants, 276 with CVD), decreases were 37.8, 3.7, 6.7, 17.3 and 0.4. Mid-life BB factors were the most important for both all cause mortality and CVD; mid-life SE factors were important for all cause mortality, and early-life SE factors were important for CVD. Parental lifespan was the weakest factor.

Conclusion

As mid-life BB risk factors best explained all cause mortality and CVD, continued action to reduce these is warranted. Targeting adverse SE factors in mid-life and early-life may contribute to reducing all cause mortality and CVD risk respectively.

INTRODUCTION

Exposure to particular circumstances and experiences across the lifecourse may have a bearing on premature mortality and disease. Knowing which exposures contribute most, and when, can help design and target preventive measures.

Systematic reviews of several studies have shown that worse socioeconomic circumstances in early-life are associated with higher risk of all cause and cardiovascular disease (CVD) mortality[1] and CVD risk.[2] Additional adjustment for adult socioeconomic circumstances and/or adult risk factors generally attenuated these relationships but some association of early-life socioeconomic circumstances remained. Adult socioeconomic factors have been related to mortality in several countries.[3, 4]

Whilst personal risk factors such as smoking, raised body mass index and raised blood pressure are clearly associated with all cause mortality and CVD, there have been fewer studies on the relationships between parental risk factors and outcomes in adult offspring. There is some evidence of transgenerational effects: parental height was associated with lower risk of offspring CHD,[5] C-reactive protein was higher in non-hypertensive offspring of hypertensive parents, compared with non-hypertensive offspring of parents without hypertension;[6] higher parental body mass index was associated with less favourable levels of offspring CVD risk factors;[7] and non-obese offspring had higher C-reactive protein and higher renin if they had obese parents compared with non-obese offspring with non-obese parents.[8] Cardiovascular risk factors are known to track across generations and persist into adult life.[9]

Many studies have shown parental lifespan to be related to mortality or survival, for example in Japan,[10] the USA,[11, 12] China,[13] Sweden[14] and Iceland.[15] However, comparisons between parental lifespan and other risk factors across the lifecourse have not been made.

In this paper, we aimed to find out which type of factors were the most important for determining mortality and CVD risk: mid-life biological and behavioural factors, mid-life socioeconomic factors, parental biological and behavioural factors, early-life socioeconomic factors or parental lifespan. We used a study based in Scotland with information at different stages of the lifecourse, and excellent information on both parents.

METHODS

The Midspan Family Study began in 1996[16] and involved adult offspring of couples who were both part of the Renfrew & Paisley prospective cohort recruited in 1972-1976.[17] Renfrew & Paisley participants (7049 men and 8353 women) were residents of the two towns, aged 45-64 years at screening, and included 4064 known married couples. The offspring cohort consisted of 2338 participants (1040 men and 1298 women, aged 30-59) from 1477 families, a 73% individual and a 84% family response.[18] Participants in both studies completed a questionnaire and attended a screening examination. The questionnaire included questions on smoking habit, occupation and home address for both generations, and alcohol consumption, exercise, accommodation, car availability, childhood accommodation, car availability in childhood, education and number of siblings for the offspring generation only. Smoking was defined as never, current or former. Social

class was derived from occupation[19, 20] and used as a continuous variable from 1-6. Social class was defined by the Registrar General's Social Class Schema of I (Professional etc), II (Intermediate), IIIN (Skilled non manual), IIIM (Skilled manual), IV (Partly-skilled) and V (Unskilled). As father's social class was missing for 20 offspring, mother's social class was used for 15, and offspring-reported father's social class used for five offspring. Carstairs deprivation category was derived from the home address and defined as a continuous variable from 1 (least deprived) to 7 (most deprived).[21] Alcohol consumption was obtained from a detailed report of the previous week's drinking and translated into units per week.[22] High alcohol consumption was defined as >28 units per week for men and >21 units per week for women. No exercise was classified as being not very or not at all physically active during usual daily activities and being physically active outside work less than once a week or never.[16] Accommodation in adulthood and childhood was defined as owner-occupied or not, and overcrowding as number of residents greater than or equal to number of rooms.[23] Car availability was defined as one or more cars in the household versus none, and childhood car availability as parental use of a car when the participant was under 16 years.[23] Education was defined as the highest level completed (tertiary or school), years of education, number of Standard grades or O levels (qualifications at age 16) and number of Highers or A levels (qualifications at age 17 or 18).[24]

At the screening examination for both generations, blood pressure, height, weight and forced expiratory volume in one second (FEV1) were recorded and non-fasting plasma cholesterol measured from a blood sample.[16, 17] Body mass index was defined as weight (in kg) divided by height (in m) squared. Percent predicted FEV1 was defined as actual FEV1 as a percentage of expected FEV1, derived from regression equations based on healthy participants.[25, 26] Additional variables, more recently identified as risk factors were measured only in the offspring cohort: high-density lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein, creatinine, glucose, leg length, waist and hip from which waist-hip ratio was derived.[27, 28]

Offspring and parents were followed-up for mortality and embarkation (leaving the UK) by flagging at the NHS Central Register which provided dates and causes of death to the end of 2011. Offspring were linked to the Scottish Morbidity Records (SMR) database from screening to the end of 2011. This is a computerised database of all hospital discharges in Scotland. International Classification of Diseases (ICD) version 9 codes 390-459 or ICD version 10 codes I00 – I99, G45 or R58 defined CVD deaths and hospital discharges. Two offspring who did not give permission to follow progress through medical records were excluded from CVD analyses.

Father's and mother's lifespan were defined as age at death if deceased or age at end of 2011 if still alive, as in previous studies.[12, 29]

Statistical methods

Non-normal variables (triglycerides and C-reactive protein) were log transformed. Variables were assigned to five groups: mid-life biological and behavioural factors, mid-life socioeconomic factors, parental biological and behavioural factors, early-life socioeconomic factors and parental lifespan. Cox proportional hazards models were used to analyse the contribution of the factors in explaining all cause mortality or CVD (defined as main diagnosis of a hospital discharge or CVD death) in offspring. Survival was from date of screening to death, embarkation or the end of 2011 for mortality analyses, and additionally to hospital discharge for the CVD analyses, whichever was first.

Proportional hazards assumptions were verified by inspection of Schoenfeld residuals. As tests for interaction with sex were not significant (p=0.27 for all cause mortality and p=0.24 for CVD), models were run with both sexes combined. Null models adjusting for age and sex were run first. Next, each risk factor was added separately to the null model. As there were missing data for some variables, the null models were re-run excluding participants with that missing variable. The best variables were selected by inspecting statistical significance and the decrease in Akaike's Information Criterion (AIC).[30] AIC is a measure of goodness-of-fit of models, with better fit indicated by smaller AIC. It is defined by (-2 x maximised log likelihood) + (2 x number of parameters estimated). The best variables were added to the null model for each of the five groups separately and the decrease in AIC noted. To ensure comparability, these analyses were restricted to participants with no missing data for all the selected variables. Both father's and mother's lifespan were included in parental lifespan models. Hazard ratios were calculated for one standard deviation increase for most continuous variables. Analyses were carried out using Stata release 11, adjusting for clustering of offspring within families. Excluded from all analyses were 30 offspring who had been adopted or were step children, leaving 2308 participants in this study.

RESULTS

There were 2092 (90.6%) offspring whose fathers had died between the ages of 47 and 98, and 1770 (76.7%) offspring whose mothers had died between the ages of 50 and 98. Fathers were still alive for 216 (9.4%) offspring (and aged between 83 and 100) and mothers were still alive for 538 (23.3%) offspring (and aged between 81 and 99). There were 132 (5.7%) deaths in 2308 offspring in the follow-up period. For each variable, AIC for the null model (adjusted for age and sex), AIC for the model which included the variable, and the decrease in AIC between the two models are shown in table 1. Particularly large decreases in AIC were seen for C-reactive protein, FEV1, % predicted FEV1, smoking and car availability. Some variables did not improve the model fit (eg cholesterol, exercise). All the mid-life socioeconomic factors improved the model fit.

Table 1. Decrease in AIC when adding each variable separately to null model for all cause mortality

N=2308 with 132 deaths (excludes 30 step/adopted offspring)

Risk factor	Units	N	AIC null	AIC	Decrease in AIC
Mid-life biological and behavioural factors					
*Systolic blood pressure	mmHg	2283	1970.1	1966.5	3.6
*Diastolic blood pressure	mmHg	2283	1970.1	1961.1	9
Cholesterol	mmol/l	2234	1894.0	1894.7	-0.7
HDL cholesterol	mmol/l	1938	1474.5	1475.9	-1.4

*Triglycerides (logarithm)	mmol/l	2228	1878.3	1873.9	4.4
*C-reactive protein (logarithm)	mg/l	2078	1772.0	1752.5	19.5
*Creatinine	µmol/l	2180	1795.5	1795.7	-0.2
*Glucose	mmol/l	2239	1893.8	1892.6	1.2
Height	m	2307	1972.1	1973.0	-0.9
Leg length	m	2300	1970.9	1972.1	-1.2
Body mass index	kg/m^2	2291	1971.6	1972.0	-0.4
*Waist-hip ratio	-	2285	1953.9	1951.1	2.8
*FEV1	l	2230	1846.8	1807.3	39.5
*% predicted FEV1	%	2230	1846.8	1801.0	45.8
*Smoking	never, current, former	2308	1972.1	1935.9	36.2
*Alcohol	units/week	2308	1972.1	1962.4	9.7
*High alcohol	1=yes; 0=no, defined as >28 units/week for men, >21 for women	2308	1972.1	1967.0	5.1
No exercise	1=yes; 0=no	2305	1971.5	1973.5	-2
Mid-life socioeconomic factors					
*Social class	1-6	2308	1972.1	1964.9	7.2
*Deprivation category	1-7	2303	1971.8	1963.8	8
*Accommodation group	1=owner-occupier; 0=not owner-occupier	2308	1972.1	1949.1	23
*Overcrowding	1=yes; 0=no, defined as people≥rooms	2307	1972.0	1965.4	6.6
*Car available for use	1=1 or more; 0=none	2306	1971.9	1954.2	17.7
Parental biological and behavioural factors					
Father's systolic blood pressure	mmHg	2308	1972.1	1971.0	1.1
*Father's diastolic blood pressure	mmHg	2308	1972.1	1968.4	3.7
Father's cholesterol	mmol/l	2292	1928.2	1929.5	-1.3
Father's height	m	2305	1958.3	1958.3	0
Father's body mass index	kg/m^2	2305	1958.3	1960.0	-1.7
*Father's FEV1	l	2308	1972.1	1969.6	2.5
Father's % predicted FEV1	%	2305	1958.3	1958.7	-0.4
Father's smoking	never, current, former	2308	1972.1	1973.0	-0.9
Mother's systolic blood	mmHg	2308	1972.1	1974.0	-1.9

pressure					
Mother's diastolic blood pressure	mmHg	2308	1972.1	1973.9	-1.8
Mother's cholesterol	mmol/l	2278	1955.3	1957.2	-1.9
*Mother's height	m	2307	1958.5	1955.6	2.9
Mother's body mass index	kg/m^2	2305	1958.1	1960.0	-1.9
*Mother's FEV1	l	2308	1972.1	1960.6	11.5
*Mother's % predicted FEV1	%	2306	1944.0	1938.2	5.8
Mother's smoking	never, current, former	2308	1972.1	1971.2	0.9
Early-life socioeconomic factors					
*Father's social class	1-6	2308	1972.1	1966.0	6.1
Father's deprivation category	1-7	2308	1972.1	1972.1	0
Childhood accommodation	1=owner-occupier; 0=not owner-occupier	2305	1938.3	1939.5	-1.2
Childhood overcrowding	1=yes; 0=no, defined as people≥rooms	2306	1955.4	1954.2	1.2
*Car available in childhood	1=yes; 0=no	2307	1972.0	1966.8	5.2
Higher education	1=tertiary; 0=school	2302	1971.7	1970.4	1.3
Years of education	years	2304	1971.8	1971.2	0.6
*Standard grades/O levels	number	2307	1972.1	1962.7	9.4
Highers/A levels	number	2307	1972.1	1971.5	0.6
*Siblings	number	2308	1972.1	1971.1	1
Parental lifespan					
*Father's lifespan	years	2306	1972.0	1965.2	6.8
Mother's lifespan	years	2307	1972.0	1971.3	0.7

*variable significant in Cox regression analysis

Akaike's Information Criterion (AIC) is measure of model fit. Better model has lower AIC

Null model adjusts for age and sex

There were 368 (16.0%) participants with a hospital discharge or death from CVD (table 2). Large decreases in AIC were seen for HDL cholesterol, C-reactive protein, waist-hip ratio, FEV1, % predicted FEV1 and father's deprivation category. Again, each of the mid-life socioeconomic factors improved the model fit. Some of the mother's biological and behavioural factors (diastolic blood

pressure, body mass index, FEV1 and % predicted FEV1) improved the model fit but none of the father's biological and behavioural factors did.

Table 2. Decrease in AIC when adding each variable separately to null model for CVD mortality or hospital admission

N=2306 with 368 participants with cardiovascular disease from hospital admission or mortality (excludes 30 step/adopted offspring and 2 with no permission to follow progress through medical records)

Risk factor	Units	N	AIC null	AIC	Decrease in AIC
Mid-life biological and behavioural factors					
*Systolic blood pressure	mmHg	2281	5499.9	5496.1	3.8
*Diastolic blood pressure	mmHg	2281	5499.9	5493.7	6.2
Cholesterol	mmol/l	2234	5394.8	5396.1	-1.3
*HDL cholesterol	mmol/l	1938	4392.9	4377.3	15.6
*Triglycerides (logarithm)	mmol/l	2228	5392.8	5380.9	11.9
*C-reactive protein (logarithm)	mg/l	2078	5057.3	5029.8	27.5
Creatinine	µmol/l	2180	5269.9	5271.8	-1.9
*Glucose	mmol/l	2239	5411.6	5404.0	7.6
Height	m	2305	5570.1	5570.9	-0.8
Leg length	m	2299	5553.1	5553.9	-0.8
*Body mass index	kg/m^2	2289	5532.9	5524.6	8.3
*Waist-hip ratio	-	2283	5514.8	5489.8	25
*FEV1	l	2229	5423.3	5404.8	18.5
*% predicted FEV1	%	2229	5423.3	5394.5	28.8
*Smoking	never, current, former	2306	5570.4	5558.4	12
Alcohol	units/week	2306	5570.4	5568.9	1.5
*High alcohol	1=yes; 0=no defined as >28 units/week for men, >21 for women	2306	5570.4	5568.1	2.3
No exercise	1=yes; 0=no	2303	5554.7	5555.7	-1
Mid-life socioeconomic factors					
*Social class	1-6	2306	5570.4	5559.3	11.1
*Deprivation category	1-7	2301	5552.0	5545.3	6.7
*Accommodation group	1=owner-occupier;	2306	5570.4	5557.3	13.1

	0=not owner-occupier				
*Overcrowding	1=yes; 0=no, defined as people≥rooms	2305	5569.9	5567.2	2.7
*Car available for use	1=1 or more; 0=none	2304	5569.7	5565.3	4.4
Parental biological and behavioural factors					
Father's systolic blood pressure	mmHg	2306	5570.4	5571.4	-1
Father's diastolic blood pressure	mmHg	2306	5570.4	5570.2	0.2
Father's cholesterol	mmol/l	2290	5476.6	5477.8	-1.2
Father's height	m	2303	5553.9	5555.8	-1.9
Father's body mass index	kg/m^2	2303	5553.9	5555.9	-2
Father's FEV1	l	2306	5570.4	5571.2	-0.8
Father's % predicted FEV1	%	2303	5553.9	5555.1	-1.2
Father's smoking	never, current, former	2306	5570.4	5574.1	-3.7
Mother's systolic blood pressure	mmHg	2306	5570.4	5569.9	0.5
*Mother's diastolic blood pressure	mmHg	2306	5570.4	5564.9	5.5
Mother's cholesterol	mmol/l	2276	5483.7	5485.5	-1.8
Mother's height	m	2305	5570.3	5569.5	0.8
*Mother's body mass index	kg/m^2	2303	5569.4	5559.2	10.2
*Mother's FEV1	l	2306	5570.4	5562.1	8.3
*Mother's % predicted FEV1	%	2304	5555.5	5551.9	3.6
Mother's smoking	never, current, former	2306	5570.4	5574.2	-3.8
Early-life socioeconomic factors					
Father's social class	1-6	2306	5570.4	5568.0	2.4
*Father's deprivation category	1-7	2306	5570.4	5553.6	16.8
Childhood accommodation	1=owner-occupier; 0=not owner-occupier	2303	5538.8	5539.0	-0.2
*Childhood overcrowding	1=yes; 0=no, defined as people≥rooms	2306	5555.0	5541.1	13.9
*Car available in childhood	1=yes; 0=no	2305	5569.9	5566.6	3.3
Higher education	1=tertiary;	2300	5554.1	5552.4	1.7

	0=school				
*Years of education	years	2302	5569.3	5563.2	6.1
*Standard grades/O levels	number	2305	5570.1	5555.8	14.3
*Highers/A levels	number	2305	5570.1	5565.4	4.7
Siblings	number	2306	5570.4	5569.6	0.8
Parental lifespan					
Father's lifespan	years	2304	5569.8	5568.5	1.3
*Mother's lifespan	years	2305	5570.0	5563.7	6.3

*variable significant in Cox regression analysis

Akaike's Information Criterion (AIC) is measure of model fit. Better model has lower AIC

Null model adjusts for age and sex

Variables which were significant and improved the model fit in the individual variable models were selected for the next set of models using groups. The variable resulting in the largest decrease in AIC was chosen where there were similar variables which could be highly correlated, such as systolic and diastolic blood pressure. Analyses for all groups were conducted with complete data for all the selected variables (1997 participants with 111 deaths in the all cause mortality analysis; 1736 participants, 276 with CVD in the CVD analysis). Hazard ratios and 95% confidence intervals for all cause mortality for each group of variables (mid-life biological and behavioural factors, mid-life socioeconomic factors, parental biological and behavioural factors, early-life socioeconomic factors and parental lifespan) are shown in table 3 and for CVD in table 4. AICs for each model, including the null model, are shown.

Table 3. Hazard ratios for all cause mortality models including best variables, excluding missing of these variables (N=1997, 111 deaths)

Variable	**Hazard ratio* (95% confidence interval)**
Null model, AIC=1629.0	
Age (years)	1.11 (1.08 – 1.15)
Sex (1=male; 0=female)	1.63 (1.12 – 2.36)
Mid-life biological and behavioural factors model, AIC=1573.2	
Age (years)	1.09 (1.05 – 1.12)
Sex (1=male; 0=female)	1.09 (0.64 – 1.86)
Diastolic blood pressure	1.23 (1.0 – 1.52)
Triglycerides (logarithm)	1.07 (0.84 – 1.35)
C-reactive protein (logarithm)	1.19 (0.96 – 1.47)
Glucose	1.13 (1.01 – 1.27)
Waist-hip ratio	0.91 (0.70 – 1.18)
% predicted FEV1	0.67 (0.56 – 0.80)

Former smoker	1.34 (0.79 – 2.29)
Current smoker	2.42 (1.52 – 3.87)
Alcohol (units/week)	1.20 (1.01 – 1.44)
Mid-life socioeconomic model, AIC=1607.4	
Age (years)	1.11 (1.08 – 1.15)
Sex (1=male; 0=female)	1.59 (1.10 – 2.30)
Social class (per social class)	1.08 (0.93 – 1.25)
Deprivation category (per depcat)	1.10 (0.96 – 1.26)
Accommodation group (1=owner-occupier; 0=not owner-occupier)	0.58 (0.35 – 0.97)
Overcrowding (1=yes; 0=no)	1.61 (0.98 – 2.64)
Car available for use (1=1 or more; 0=none)	0.67 (0.39 – 1.17)
Parental biological and behavioural factors model, AIC=1618.7	
Age (years)	1.10 (1.06 – 1.13)
Sex (1=male; 0=female)	1.62 (1.12 – 2.35)
Father's diastolic blood pressure	1.22 (1.02 – 1.45)
Father's FEV1	0.88 (0.72 – 1.07)
Mother's height	0.87 (0.72 – 1.06)
Mother's FEV1	0.80 (0.65 – 0.97)
Early-life socioeconomic factors model, AIC=1621.7	
Age (years)	1.09 (1.05 – 1.13)
Sex (1=male; 0=female)	1.70 (1.17 – 2.47)
Father's social class (per social class)	1.17 (0.97 – 1.40)
Car available in childhood (1=yes; 0=no)	0.77 (0.50 – 1.16)
Standard grades/O levels (per Standard grade/O level)	0.91 (0.84 – 0.99)
Siblings (per sibling)	1.02 (0.93 – 1.12)
Parental lifespan model, AIC=1623.1	
Age (years)	1.12 (1.08 – 1.16)
Sex (1=male; 0=female)	1.61 (1.11 – 2.33)
Father's lifespan (per 5 years)	0.88 (0.81 – 0.97)
Mother's lifespan (per 5 years)	0.92 (0.83 – 1.02)

* For continuous variables, hazard ratios represent 1 standard deviation increase unless otherwise stated

Table 4. Hazard ratios for CVD models including best variables, excluding missing of these variables (N=1736, 276 with CVD mortality or CVD hospital admission)

Variable	Hazard ratio* (95% confidence interval)
Null model, AIC=4016.4	
Age (years)	1.06 (1.04 – 1.08)
Sex (1=male; 0=female)	1.58 (1.25 – 2.0)
Mid-life biological and behavioural factors model, AIC=3978.6	
Age (years)	1.05 (1.02 – 1.07)
Sex (1=male; 0=female)	1.02 (0.70 – 1.49)
Diastolic blood pressure	1.03 (0.90 – 1.18)
HDL cholesterol	0.75 (0.64 – 0.88)
Triglycerides (logarithm)	1.0 (0.83 – 1.20)
C-reactive protein (logarithm)	1.19 (1.04 – 1.35)
Glucose	1.09 (1.0 – 1.20)
Body mass index	0.96 (0.82 – 1.12)
Waist-hip ratio	1.15 (0.94 – 1.39)
% predicted FEV1	0.85 (0.75 – 0.97)
Former smoker	1.0 (0.74 – 1.35)
Current smoker	1.26 (0.94 – 1.70)
High alcohol (1=yes; 0=no)	1.17 (0.83 – 1.67)
Mid-life socioeconomic model, AIC=4012.7	
Age (years)	1.06 (1.04 – 1.08)
Sex (1=male; 0=female)	1.56 (1.23 – 1.99)
Social class (per social class)	1.07 (0.97 – 1.19)
Deprivation category (per depcat)	1.03 (0.95 – 1.13)
Accommodation group (1=owner-occupier; 0=not owner-occupier)	0.74 (0.52 – 1.05)
Overcrowding (1=yes; 0=no)	1.29 (0.92 – 1.82)
Car available for use (1=1 or more; 0=none)	1.03 (0.72 – 1.49)
Parental biological and behavioural factors model, AIC=4009.7	
Age (years)	1.05 (1.03 – 1.07)
Sex (1=male; 0=female)	1.57 (1.24 – 1.99)
Mother's diastolic blood pressure	1.09 (0.97 – 1.22)
Mother's body mass index	1.15 (1.02 – 1.29)
Mother's FEV1	0.92 (0.81 – 1.05)
Early-life socioeconomic factors model, AIC=3999.1	
Age (years)	1.04 (1.02 – 1.07)
Sex (1=male; 0=female)	1.61 (1.27 – 2.05)
Father's deprivation category (per depcat)	1.13 (1.03 – 1.24)
Childhood overcrowding (1=yes; 0=no)	1.54 (1.07 – 2.21)
Car available in childhood (1=yes; 0=no)	0.96 (0.74 – 1.24)
Standard grades/O levels (per Standard grade/O	0.95 (0.91 – 0.99)

level)

Parental lifespan model, AIC=4016.0	
Age (years)	1.06 (1.04 – 1.08)
Sex (1=male; 0=female)	1.57 (1.24 – 1.98)
Father's lifespan (per 5 years)	0.97 (0.92 – 1.03)
Mother's lifespan (per 5 years)	0.94 (0.88 – 1.0)

* For continuous variables, hazard ratios represent 1 standard deviation increase unless otherwise stated

Table 5 summarises the decreases in AIC for each model compared to the AIC for null models, from tables 3 and 4. For both all cause mortality and CVD, the largest decrease in AIC was for mid-life biological and behavioural factors, meaning that this group was the most important for both these causes. In both cases, the decrease was substantially greater than with the other groups. For all cause mortality, the next most important was for mid-life socioeconomic factors, followed by parental biological and behavioural factors, early-life socioeconomic factors and parental lifespan. Apart from the most important group, results for CVD were different from those for all cause mortality, with the second most important group being early-life socioeconomic factors, followed by parental biological and behavioural factors, mid-life socioeconomic factors and parental lifespan. These last three groups had markedly smaller decreases in AIC (6.7, 3.7 and 0.4), compared with the first two (37.8 and 17.3).

Table 5. Summary of decreases in AIC for all cause mortality and CVD when all best variables are included, excluding missing of these variables

Model	All cause mortality	CVD
N	1997	1736
Cases	111	276
	Decrease in AIC	
Mid-life biological and behavioural factors	55.8	37.8
Mid-life socioeconomic factors	21.6	3.7
Parental biological and behavioural factors	10.3	6.7
Early-life socioeconomic factors	7.3	17.3
Parental lifespan	5.9	0.4

DISCUSSION

In this well-defined cohort study of adult offspring with information at different stages of the lifecourse and on both parents, biological and behavioural factors in mid-life were the most important factors for risk of all cause mortality and CVD. Although this was not unexpected, the large size of the decrease in AIC compared to the other groups of factors was of interest.

Mid-life socioeconomic factors were the next most important for all cause mortality, but early-life socioeconomic factors were the next most important for CVD. Previous studies have shown relationships between adult socioeconomic factors and all cause mortality and CVD,[3, 4] and early-life socioeconomic factors and all cause mortality and CVD.[1, 2] In Finland a study of nearly 24 000 men and women found childhood adversity was associated with incident CVD (hospital admission or death) in adulthood, especially in women.[31] In the British Regional Heart Study of 5552 men aged 52-74, the effect of adverse childhood socioeconomic circumstances on fatal or non-fatal coronary heart disease (CHD) risk persisted in older age.[32]

Parental biological and behavioural factors were the third most important group for both all cause mortality and CVD, performing better than early-life socioeconomic factors for all cause mortality, and better than mid-life socioeconomic factors for CVD. There have been some studies of intergenerational effects. In the 1958 British Birth Cohort, higher parental body mass index was associated with less favourable levels of offspring CVD risk factors, such as C-reactive protein.[7] In a previous analysis of this cohort, greater parental height was associated with lower risk of offspring CHD, more strongly in mothers than fathers, suggesting possible intra-uterine mechanisms.[5] In the current study, mother's height was included in the all cause mortality model but not in the CVD model. Mother's body mass index, mother's FEV1 and mother's diastolic blood pressure were selected for the CVD model, but not mother's height which had resulted in a very small decrease in AIC.

In the current study, parental lifespan explained the smallest amount of all cause mortality and CVD, compared to the other groups of factors. Other studies have shown parental lifespan to be related to mortality or survival. A large study in Japan found inverse associations between mortality from all causes (and from CVD) by father's and mother's age at death.[10] A US study of adults found a survival benefit to offspring for each extra decade of parental survival.[12] A study from China found that familial transmission of longevity existed at very old ages.[13] A study of over 6000 men in Sweden found an inverse association between mortality and father's age at death and a weaker association with mother's age at death.[14] A study of the whole population of Iceland including ancestors suggested a familial component to longevity which could be genetic.[15] Parental lifespan, especially mother's lifespan, was positively associated with better cognitive functioning and inversely associated with self-reported chronic diseases in later life in a cohort of older men and women.[29] The usefulness of parental lifespan as a predictor of mortality depends on what other factors are available; in this study other factors have been shown to be better predictors. From a public health perspective, reduced parental lifespan cannot be altered, but could act as a spur to behaviour change, and to intervention where an early parental death was heritable.

The majority of the mid-life biological and behavioural factors are modifiable at an individual level, suggesting action on these factors could help reduce mortality and CVD risk. Whilst early-life

socioeconomic factors are not modifiable at an individual level, action can be taken at a societal level, for example in education and accommodation. Negative mid-life socioeconomic factors are also modifiable with action at a policy level rather than by individuals. It is not possible to change one's parental biological and behavioural factors. It is encouraging that the group of factors with the biggest apparent impact on mortality is probably the easiest to modify.

Strengths

There were several more recently identified risk factors available (for example triglycerides, C-reactive protein and waist-hip ratio). Unlike other studies, this study did not depend on adult recall for parental risk factors, parental lifespan and some early socioeconomic markers (father's social class and father's deprivation category). Adult recall of father's social class has been shown to underestimate the real associations[33] and offspring recall of parental lifespan could be incorrect.[29] Its main strength is the availability of data for both parents including parental lifespan, in addition to lifecourse data on the participants.

Limitations

The Family study is not fully representative of the general population since its participants were offspring of parents who had both taken part in an earlier study. Since that study included men and women aged 45–64 years, they had to have survived to at least 45 years to take part. Family study participants were likely to be more advantaged and healthier than people who did not grow up with both parents.[34] The participants were offspring from a regional cohort in the west of Scotland, so these results may not be generalisable to other populations. They were healthier than participants of Scottish and English studies conducted around the same time.[16] The main analyses were complete case analyses but no differences were found between the group of participants with missing data and the group included in the analyses, except for sex in the CVD analysis, where 53.0% (95% confidence interval 48.9% - 57.1%) of the group with missing data were men and 41.6% (39.3% - 43.9%) of the group included in the analysis were men. Thus the results and conclusions were unlikely to have been affected by the exclusions.

Since only 5.7% of participants have died, any associations may be different with longer-term follow-up. The associations found in this study cannot be considered causal. Biological and behavioural factors, such as smoking, are known to be socially patterned, whether by adult or early-life socioeconomic circumstances,[35-37] so our groups are not independent, and biological and behavioural factors may be on causal pathways influenced by socioeconomic or cultural factors.[38] Biological and behavioural factors were measured in mid-life but some, such as height and FEV1, are due to influences across the lifecourse. Risk factors, especially when measured longitudinally can explain part of the social gradient in mortality[39] and the current study was limited to one screening. Although AIC may not be able to detect non-linearities,[40] it is suitable for comparing models as in this study.

Conclusions

These analyses have shown that there are multiple influences on health across the lifespan. As mid-life biological and behavioural factors best explained both all cause mortality and CVD, continued

public health action to reduce these appears warranted. Targeting adverse socioeconomic factors in mid-life and early-life may contribute to reducing all cause mortality and CVD risk respectively.

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The Privacy Advisory Committee of ISD Scotland gave permission for use of the hospital discharge data.

ETHICAL APPROVAL OF RESEARCH

Ethical approval for the Family study was granted by the Argyll and Clyde Local Research Ethics Committee (Ref LREC 11/95).

Participants gave full consent before taking part.

DATA SHARING

Permission for use of data is via the Midspan steering committee

Licence for Publication

COMPETING INTERESTS

None declared

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BOX

What is already known on this subject?

Socioeconomic, behavioural and biological risk factors have all been associated with mortality and cardiovascular disease (CVD) at different times of the lifecourse. Parental risk factors and parental lifespan may also have effects.

What this study adds?

For both all cause mortality and CVD, own biological and behavioural factors were the strongest factors, and parental lifespan the weakest. Of next importance were mid-life socioeconomic factors for all cause mortality and early life socioeconomic factors for CVD. This suggests continued public health action to reduce own biological and behavioural factors. Targeting adverse socioeconomic factors in mid-life and early-life may help reduce mortality and CVD risk respectively.

References

1 Galobardes B, Lynch J, Davey Smith G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. *Epidemiol Rev* 2004;**26**:7-21.

2 Galobardes B, Davey Smith G, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. *Ann Epidemiol* 2006;**16**:91-104.

3 Mackenbach JP, Stirbu I, Roskam AR*, et al.* Socioeconomic inequalities in health in 22 European Countries. *N Engl J Med* 2008;**358**:2468-81.

4 Puddu PE, Menotti A, Tolonen H*, et al.* Determinants of 40-year all-cause mortality in the European cohorts of the Seven Countries Study. *Eur J Epidemiol* 2011;**26**:595-608.

5 Gray L, Davey Smith G, McConnachie A*, et al.* Parental height in relation to coronary heart disease: examining transgenerational influences on health using the west of Scotland Midspan Family Study. *Int J Epidemiol* 2012;**41**:1776-85.

6 Lieb W, Pencina MJ, Wang TJ*, et al.* Association of parental hypertension with concentrations of select biomarkers in nonhypertensive offspring. *Hypertension* 2008;**52**:381-6.

7 Cooper R, Pinto Pereira SM, Power C*, et al.* Parental obesity and risk factors for cardiovascular disease among their offspring in mid-life: findings from the 1958 British Birth Cohort Study. *Int J Obes* 2013;**37**:1590-6.

8 Lieb W, Pencina MJ, Lanier KJ*, et al.* Association of parental obesity with concentrations of select systemic biomarkers in nonobese offspring. The Framingham Heart study. *Diabetes* 2009;**58**:134-7.

9 Vik KL, Romundstad P, Nilsen TIL. Tracking of cardiovascular risk factors across generations: family linkage within the population-based HUNT study, Norway. *J Epidemiol Community Health* 2013;**67**:564-70.

10 Ikeda A, Iso H, Toyoshima H*, et al.* Parental longevity and mortality amongst Japanese men and women: the JACC Study. *J Intern Med* 2006;**259**:285-95.

11 Smith KR, Mineau GP, Garibotti G*, et al.* Effects of childhood and middle-adulthood family conditions on later-life mortality: Evidence from the Utah Population Database, 1850-2002. *Soc Sci Med* 2009;**68**:1649-58.

12 Klein BEK, Lee KE, Klein R. Attained parental age and children's survival at mid-life ages in a large population. *Gerontology* 2007;**53**:399-403.

13 You D, Gu D, Yi Z. Familial transmission of human longevity among the oldest-old in China. *J Appl Gerontol* 2010;**29**:308-32.

14 Rosengren A, Thelle D, Wilhelmsen L. Parental age and coronary disease in the general male population. *J Intern Med* 2002;**251**:258-67.

15 Gudmundsson H, Gudbjartsson DF, Kong A*, et al.* Inheritance of human longevity in Iceland. *Eur J Hum Genet* 2000;**8**:743-9.

16 Hart C, McConnachie A, Upton M*, et al.* Risk factors in the Midspan family study by social class in childhood and adulthood. *Int J Epidemiol* 2008;**37**:604-14.

17 Hawthorne VM, Watt GCM, Hart CL*, et al.* Cardiorespiratory disease in men and women in urban Scotland: baseline characteristics of the Renfrew/Paisley (Midspan) Study population. *Scott Med J* 1995;**40**:102-7.

18 Upton M, McConnachie A, McSharry C*, et al.* Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000;**321**:88-92.

19 General Register Office. *Classification of Occupations 1966*. London: HMSO 1966.

20 General Register Office. *Classification of Occupations 1990*. London: HMSO 1990.

21 Carstairs V, Morris R. *Deprivation and Health in Scotland.* Aberdeen: Aberdeen University Press 1991.

22 Hart CL, Davey Smith G, Upton MN*, et al.* Alcohol consumption behaviours and social mobility in men and women of the Midspan Family study. *Alcohol Alcohol* 2009;**44**:332-6.

23 Talwar D, McConnachie A, Welsh P*, et al.* Which circulating antioxidant vitamins are confounded by socioeconomic deprivation? The Midspan Family Study. *PLoS One* 2010;**5**:e11312.

24 Hart CL, Deary IJ, Davey Smith G*, et al.* Childhood IQ of parents related to characteristics of their offspring: linking the Scottish Mental Survey 1932 to the Midspan Family Study. *J Biosoc Sci* 2005;**37**:623-39.

25 Hole DJ, Watt GCM, Davey Smith G*, et al.* Impaired lung function and mortality risk in men and women: Findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;**313**:711-6.

26 Upton M, Davey Smith G, McConnachie A*, et al.* Maternal and personal cigarette smoking synergize to increase airflow limitation in adults. *Am J Respir Crit Care Med* 2004;**169**:479-87.

27 Lowe GDO, Upton MN, Rumley A*, et al.* Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein. *Thromb Haemost* 2001;**86**:550-6.

28 Gunnell D, Whitley E, Upton M*, et al.* Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. *J Epidemiol Community Health* 2003;**57**:141-6.

29 Gjonca E, Zaninotto P. Blame the parents? The association between parental longevity and successful ageing. *Demographic Res* 2008;**19**:1435-50.

30 Akaike H. A new look at the statistical model identification. *IEEE T Automat Contr* 1974;**AC-19**:716-23.

31 Korkeila J, Vahtera J, Korkeila K*, et al.* Childhood adversities as predictors of incident coronary heart disease and cerebrovascular disease. *Heart* 2010;**96**:298-303.

32 Ramsay SE, Whincup PH, Morris RW*, et al.* Are childhood socio-economic circumstances related to coronary heart disease risk? Findings from a population-based study of older men. *Int J Epidemiol* 2007;**36**:560-6.

33 Batty GD, Lawlor DA, Macintyre S*, et al.* Accuracy of adults' recall of childhood social class: findings from the Aberdeen children of the 1950s study. *J Epidemiol Community Health* 2005;**59**:898-903.

34 Lundberg O. The impact of childhood living conditions on illness and mortality in adulthood. *Soc Sci Med* 1993;**36**:1047-52.

35 Davey Smith G, Hart CL, Watt G*, et al.* Individual social class, area-based deprivation, cardiovascular disease risk factors and mortality : the Renfrew and Paisley study. *J Epidemiol Community Health* 1998;**52**:399-405.

36 Davey Smith G, Hart C, Hole D*, et al.* Education and occupational social class: which is the more important indicator of mortality risk? *J Epidemiol Community Health* 1998;**52**:153-60.

37 Giesinger I, Goldblatt P, Howden-Chapman P*, et al.* Association of socioeconomic position with smoking and mortality: the contribution of early life circumstances in the 1946 birth cohort. *J Epidemiol Community Health* 2014;**68**:275-9.

38 Power C, Matthews S. Origins of health inequalities in a national population sample. *Lancet* 1997;**350**:1584-9.

39 Stringhini S, Sabia S, Shipley M*, et al.* Association of socioeconomic position with health behaviors and mortality. *JAMA* 2010;**303**:1159-66.

40 Roberts S, Martin MA. The question of nonlinearity in the dose-response relation between particulate matter air pollution and mortality: can Akaike's Information Criterion be trused to take the right turn? *Am J Epidemiol* 2006;**164**:1242-50.