The Midspan studies

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1. How did the study come about?

The use of large scale epidemiological studies for public health research was pioneered in Scotland by Victor Hawthorne in the 1960s. The Midspan studies (so called because they were centred around the "mid-span" of life) originated in the post-war drive to control pulmonary tuberculosis using Mass Miniature Radiography. The availability of a well-established and effective method of examining large numbers of apparently healthy volunteers suggested the extension of the screening examination to detect a much wider range of chronic disease and disability. Midspan is the name given to four separate occupational and general population cohort studies based in Scotland which used Hawthorne's methodology[1].

The first study, incorporating Main and Tiree, received funding from the Board of Management for Glasgow Northern Hospitals and the Western Regional Hospital Board. It was developed in conjunction with the Whitehall study of civil servants in the Greater London area. The second study, the Collaborative Study, was undertaken as part of an international co-operative study by the European office of the WHO on the prevention of ischaemic heart disease and hypertension and was funded by the Scottish Home and Health Department. The third study, the Renfrew/Paisley Study, a general population cohort, was supported by the Renfrewshire King Edward Memorial Trust and the Scottish Home and Health Department. In the 1990s, the most recent study, the Family Study, moved on to study the offspring of couples who had taken part in the Renfrew/Paisley study, and was funded by the NHS Cardiovascular Research and Development Programme and the Wellcome Trust.

2. What does it cover, and how has this changed?

In addition to improving the detection and control of tuberculosis, the general aim was to develop an evidence base for the detection and control of cardiorespiratory risks and diseases in whole populations. The idea was to pursue the precept that a small reduction in large numbers of, say, mild asymptomatic hypertensives, would have a bigger impact on the overall health of a total population than treating the relatively small numbers of those with overt disease. Cohort studies were needed to identify and measure the risks of dying from coronary artery disease, cardiovascular diseases, lung and other cancers and respiratory disease – the main causes of excess mortality in west central compared with the rest of Scotland, and in Scotland compared with England and Wales.

The Tiree survey investigated (and confirmed) the local belief that blood pressure was higher on the island than on the mainland[2].

As the cohorts have matured, focus has changed from analyses of cardiorespiratory disease risk in relation to risk factors assessed in middle age to consideration of lifecourse influences on adult health. More recently, it has been possible to trace the adult offspring of some of the 4067 married couples who took part in the Renfrew/Paisley study, for studies of intergenerational trends and familial aggregation of cardiorespiratory risk, disease and associated behaviours.

3. Who is in the sample? and
4. How often have they been followed up?

Midspan Cohort	Details

Main and Tiree

Date	Baseline study 1964-68
Cohort (1)	Industrial group from 13 factories
Location	Central belt of Scotland
Number	3,931 (3,417 male, 514 female)
Age	15-70 years
Cohort (2)	Population cohort and relatives emigrated to mainland
Location	Isle of Tiree & Glasgow
Number	762 (338 male, 424 female)
Age	14-92 years
Follow-up	
Date	1967-70 (2-4 years after baseline)
Number Cohort (1)	1,750 (1,530 male, 220 female)
Number Cohort (2)	496 (218 male, 278 female)

Collaborative

Date	Baseline study 1970-73
Cohort	Occupational group from 27 workplaces
Location	Central belt of Scotland
Age	Working age
Number	7,028 (6,022 male, 1,006 female)
Follow-up	
Date	1977
Number	3,221 (2,760 male, 461 female)

Renfrew/Paisley

Date	1972-76
Cohort	General population (78% response rate)
Location	Neighbouring towns on the outskirts of Glasgow
Age	45-64 years
Number	15,402 (7,048 male, 8,354 female)
Follow-up	
Date (Renfrew only)	1973
Number	2,273 (1,062 male, 1,211 female)
Date (Renfrew/Paisley)	1977-79
Number	8,402 (3,724 male, 4,678 female)

Family Study

Date	1996
Cohort	Offspring of married couples in the Renfrew/Paisley cohort (73%/84% response rates individuals/families)
Location	West of Scotland
Age	30-59 years
Number	2,338 (1,040 sons, 1,298 daughters) from 1477 families.
Follow-up	In 2001 DNA was collected from 556 Renfrew/Paisley surviving parents.

5. What has been measured?

	Main and Tiree	Collaborative	Renfrew/Paisley	Family Study
Baseline	Socioeconomic	Lifecourse	Socioeconomic	Health and lifestyle

1. Self-administered questionnaire	factors Health behaviour Cardiorespiratory measures Self-reported anthropometric measures	socioeconomic factors Health behaviour Cardiorespiratory measures Stress Education	factors Health behaviour Cardiorespiratory measures General health questionnaire	including family history and 7 day food frequency data Birthweights
2. Screening check	Physiological measures Biochemical tests on urine	Anthropometric measures Physiological tests Blood and urine samples for biochemical analyses	Anthropometric measures Physiological tests Blood samples	Anthropometric measures Physiological tests Extensive laboratory tests Stored samples of serum, plasma and DNA
Follow-up	As above	As above, except for samples	As above, except for samples	
On-going	Mortality	Mortality Cancer incidence Hospital admissions	Mortality Cancer incidence Hospital admissions	Mortality Cancer incidence Hospital admissions

6. What is attrition like?

About half of the members of the early cohorts were rescreened a few years after the initial screening (48% of Main, 46% of Collaborative and 55% of Renfrew/Paisley). All cohorts have been flagged for mortality with the General Register Office and we are informed of the small number of participants who emigrate.

7. What has it found? Key findings and key publications

Population Screening: The feasibility of the mass screening examination in healthy populations in a timely and cost efficient manner was first described and demonstrated[2-4]. Compared to previous UK studies, men in Renfrew/Paisley had shorter stature, higher blood pressure, a higher proportion of smokers continuing to smoke, lower forced expiratory volume in 1 second (FEV1), more angina (Rose questionnaire), higher breathlessness on effort and more chronic bronchitis[5]. Compared to Renfrew/Paisley men, Renfrew/Paisley women had higher plasma cholesterol, lower FEV1, fewer ever smokers and higher breathlessness on effort. Compared with the Whitehall study, the Collaborative and Renfrew/Paisley cohorts had higher mortality rates but these could be explained by the higher levels of smoking, poorer socioeconomic status, lower FEV1 and shorter stature in the west of Scotland cohorts[6].

Blood pressure: The Renfrew/Paisley study made a major contribution to the debate about whether a substantial reduction of diastolic blood pressure could lead to a significant decrease in mortality[7]. It was found that two blood pressure measurements are better than one for indicating stroke risk[8].

Cholesterol: Cholesterol was not a good indicator of all cause mortality, although there was a positive and close relationship with coronary heart disease[9]. There was no relationship

between cholesterol and overall stroke[10]. However, there was a significant inverse relationship between cholesterol and haemorrhagic stroke, and a J shaped relationship between cholesterol and ischaemic stroke.

Smoking: The prevalence of respiratory symptoms increased with the number of cigarettes smoked and smokers had a mortality rate twice that of never smokers[11]. The Renfrew/Paisley cohort provided the first opportunity to examine the characteristics of a population group in Scotland in relation to their cigarette smoking habits in an area which at that time had the highest lung cancer incidence rate in the world[12]. Compared with other cohorts, the lung cancer rates were higher at all levels of cigarette smoking. Using linked data for participants living in the same household, the Renfrew/Paisley cohort was the first UK study to show the deleterious effects of passive smoking both in terms of reduced FEV1, increased symptomatology and poorer lung cancer and coronary heart disease (CHD) mortality amongst passive smokers[13].

Coronary Heart Disease: Coronary mortality in a representative population sample of women was examined and similarities with the known coronary risk factors found amongst men were established in women[14]. Another study examining the consistency of coronary risk factors for both men and women for both coronary disease and for stroke, highlighted similarities and differences[15]. CHD mortality rates over 15 years were quadrupled in people with two or more of Rose questionnaire angina, a previous history of CHD and/or ECG evidence of ischaemia[16]. Risk-mortality relationships were similar in men and women, with women having coronary events 15 years later than men. “Visible risk” (obesity and smoking) was a good predictor of CHD mortality[17]. “Unexplained” CHD deaths in men at low visible risk were rare, and usually associated with less visible risk factors. “Unwarranted survivals”, (i.e. despite being at high visible risk) were usually associated with more favourable profiles of less visible risk factors. “Exceptions to the rule” should not distract from the message that the differences in survival between high and low visible risk groups are dramatic.

Stroke: Blood pressure, smoking, cardiothoracic ratio, pre-existing heart disease and diabetes were positively related to stroke mortality in 20 years and height and FEV1 were inversely related[18]. Stroke mortality rates in former smokers were similar to never smokers. Women’s stroke mortality rates were similar to men’s, unlike coronary heart disease mortality where women had lower rates than men. Risk factors for stroke in men and women had similar relationships with stroke incidence (measured by hospital admissions data), as with stroke mortality[19]. Poorer socio-economic circumstance was associated with greater stroke risk, with early life circumstances being of particular importance[20].

Respiratory: Impaired lung function was a major clinical indicator of mortality risk in men and women for a wide range of diseases, in addition to respiratory disease, an observation also found in lifelong non-smokers[21]. The effect of maternal and paternal smoking (documented over 20 years previously) on lung function in more than 2000 adult offspring was estimated[22]. There was a graded inverse association between maternal smoking and offspring FEV1, independent of offspring smoking, and no effect of paternal smoking on offspring FEV1. The Family Study has also provided the first evidence that maternal smoking synergises with personal smoking to increase airflow limitation and chronic obstructive pulmonary disease risk[23]. Identical questions answered by parents and their adult offspring showed a two-fold increase in the prevalence of asthma between the mid-1970s and the mid-1990s, against the background of a rising prevalence of atopy[24].

Cancer: The main interest has been in lung cancer because of its high incidence locally. Analyses have established a higher risk per cigarette smoked generally in the population compared to other major cohort studies[12], an increased link with social class not explained purely by the amount smoked[25], and relationships with a range of variables, mostly

respiratory, indicating an increased susceptibility to the effects of cigarette smoke[26; 27]. Increasing non-linear risks of lung cancer with increasing tar levels have been demonstrated[28]. Repudiation of an underlying cancer risk in relation to blood pressure at a population level has been important in understanding varying cancer risks in some hypertensive patients[29; 30].

Qualitative studies about heart disease: Lay people may differ from health professionals in their perception of a family history of heart disease[31]. Working class men required a greater number of relatives to be affected before they perceived that they had a family history. Participants did not always regard themselves as being at risk if they felt different from affected relatives. CHD was perceived to be a male disease, with women remaining invisible in discourses about heart disease[32]. CHD was seen as a "good way to go", compared with a painful and lingering death[33].

Alcohol: There was no relationship between mortality from coronary heart disease and alcohol consumption, after adjustments for potential confounders[34]. Drinkers of over 35 units per week had double the risk of stroke mortality compared with non drinkers. All cause mortality was higher in men drinking 22 units per week or more.

Haemostasis: Use of hormone replacement therapy (HRT) tablets was associated with increased levels of some clotting factors (Factor IX, activated protein resistance and C-reactive protein) and reduced levels of others (tissue plasminogen activator, plasminogen activator inhibitor). Transdermal HRT (i.e. "patches") was not associated with these changes[35]. There was a negative association between birthweight and C-reactive protein in adulthood[36].

Early origins: Lower birthweight of offspring was associated with higher parental mortality from all causes and from cardiovascular disease[37]. This elevated mortality was not explained by a range of social, environmental, behavioural, and physiological risk factors. The strength of the association was greater than expected from the degree of concordance of birth weights across generations. Birthweight was positively associated with leg length, trunk length and total height[38]. Behavioural risk factors (cigarette smoking and recreational physical exercise) were more strongly associated with adult social circumstances than with childhood circumstances[39]. Physiological risk factors (diastolic blood pressure, cholesterol and FEV1) were associated to varying degrees with both childhood and adult circumstances. Having more siblings was related to adulthood disease risk, which could be explained by confounding risk factors, with the exception of stomach cancer mortality and haemorrhagic stroke[40].

Height: Taller people and those with good FEV1 experienced a reduced risk of CHD[41]. Leg length, an indicator of pre-pubertal nutritional status, was the component of height most strongly associated with risk. Height and FEV1 may both be markers of childhood exposures which influence growth and CHD risk. Greater height was associated with reduced risk of coronary heart disease, stroke and respiratory death[42]. Lung function was an important mediator of the association between height and cardiorespiratory mortality. Greater height was associated with increased risk of several cancers unrelated to smoking. The association between height and cancer may reflect the influence of calorie intake during childhood. There was a strong inverse relationship between height and haemorrhagic stroke and a weak, non-significant relationship with ischaemic stroke[43].

Social class and lifecourse: Individual (social class) and area-based (deprivation category) socioeconomic measures were independently associated with risk factors, morbidity and mortality[44]. Health and risk of premature death were determined by socioeconomic factors acting throughout life[45]. Mortality from stroke and stomach cancer was particularly dependent on social circumstances in childhood, whereas mortality from coronary heart disease and respiratory disease was dependent on social circumstances in both adulthood and childhood[46].

Mortality from accidents and violence and from lung cancer was mainly dependent on factors acting in adulthood. Socioeconomic and behavioural factors produced a cumulative influence on cardiovascular disease mortality risk[47]. Childhood and adulthood social class, smoking and heavy drinking explained about two thirds of the population burden of cardiovascular disease mortality in the west of Scotland. Occupational social class and education were both strongly associated with mortality[48]. Social environment in adulthood was the key determinant of smoking behaviour. Occupational social class was more strongly associated with overall and non-cardiovascular mortality than was the educational measure. The educational measure was more strongly associated with cardiovascular than with other causes of death.

Stress and Psychosocial Factors: Stress in day-to-day life, measured by the Reeder stress index, was related in the expected direction to behavioural risk factors, such as smoking, alcohol drinking and lack of exercise – the more stress, the worse the risk factor profile[49]. This indicates that the stress measure correctly indexed the experience of stress. However when these data were collected – in the early 1970s – people in more favourable social circumstances reported higher levels of stress. This confounding led to stress being apparently protective with respect to later mortality[50]. People who reported high levels of stress also reported more adverse experiences with respect to other health measures, such as chest pain. This led to an apparent association between stress and angina – which was also reflected in hospital admissions, since people who go to the doctor complaining of chest pain are more likely to be admitted to hospital for suspected coronary heart disease - but the association was in the other direction with objective measures of coronary heart disease – ECG ischaemia and CHD mortality[51]. This demonstrates how reporting tendency can seriously compromise the interpretations of studies relating stress to fully subjective or partly subjective health outcomes. Persistent short sleep duration was associated with elevated all-cause and cardiovascular disease mortality[52].

Hospital admissions: 79% of the Renfrew/Paisley cohort experienced at least one acute hospital stay[53]. A high proportion of acute hospital bed days were required near to the time of death. For non-survivors, 42% of all acute episodes (55% of bed days) took place during the twelve months before death. Those who were at higher risk of admission were the older members of the cohort (especially men), those with low FEV1, smokers, those who were underweight or obese, the small number with abnormal levels of blood sugar, those with high blood pressure and those who lived in the most deprived areas. Preventive programmes which impact on these determinants of ill health may be useful in reducing hospital admission rates.

8. What are the main strengths and weaknesses?

Major strengths of the Midspan studies were the very large numbers of participants and the inclusion of women, at a time when other UK epidemiological studies included only men. An unplanned consequence of the Renfrew/Paisley study as a general population study with high response rates in a defined area, was the inclusion of many married couples and the possibility of a subsequent family study. General goodwill, study loyalty and the support of local family doctors made this a reality. Having occupational as well as general population cohorts in a similar location was another strength. The Collaborative study data were particularly suited for lifecourse studies as information was collected on socioeconomic factors in childhood and early adulthood. A salient feature of the whole enterprise has been continued follow-up either by re-examination or more comprehensively, by linkage to NHS mortality, cancer and other morbidity registers. Midspan has continued to attract the interests and participation of researchers from many disciplines and centres, whose achievements are given in the main list of references.

A major weakness has been the lack of core funding. Midspan has been funded by a series of short-term grants. Continuity remains uncertain. Different variables were introduced and

dropped between studies, depending on current interests. It would have been preferable to have some of the variables that were only collected in the Collaborative study also collected in the other studies, in particular the lifecourse, stress and alcohol variables. Although the 1996 study stored blood samples for future use, no samples were stored for the original studies. Blood samples were collected from surviving parents of Family study participants in 2001, but only 556 were obtained, limiting future genetic studies.

9. Can I get hold of the data? Where can I find out more?

The data are available to experienced teams of researchers who have applied and been granted permission by the Midspan Steering Committee to use the data for a specific research proposal. Such work is conducted in collaboration with the Midspan team.

For further details on how to apply for access to the data see -
Procedure for Requests for Use of MIDSPAN Data in the Research section of the Midspan website: http://www.gla.ac.uk/faculties/medicine/midspan/

10. A complete list of publications

This will go on the online version of the journal.

List of proposed figures

Figure 1 Victor Hawthorne in 1970

Figure 2 Midspan screening vehicle arriving at Scarinish harbour, Tiree 1967

Figure 3 Lung function testing for the Family Study

Figure 4 Midspan logo

Figure 5 Family Study logo

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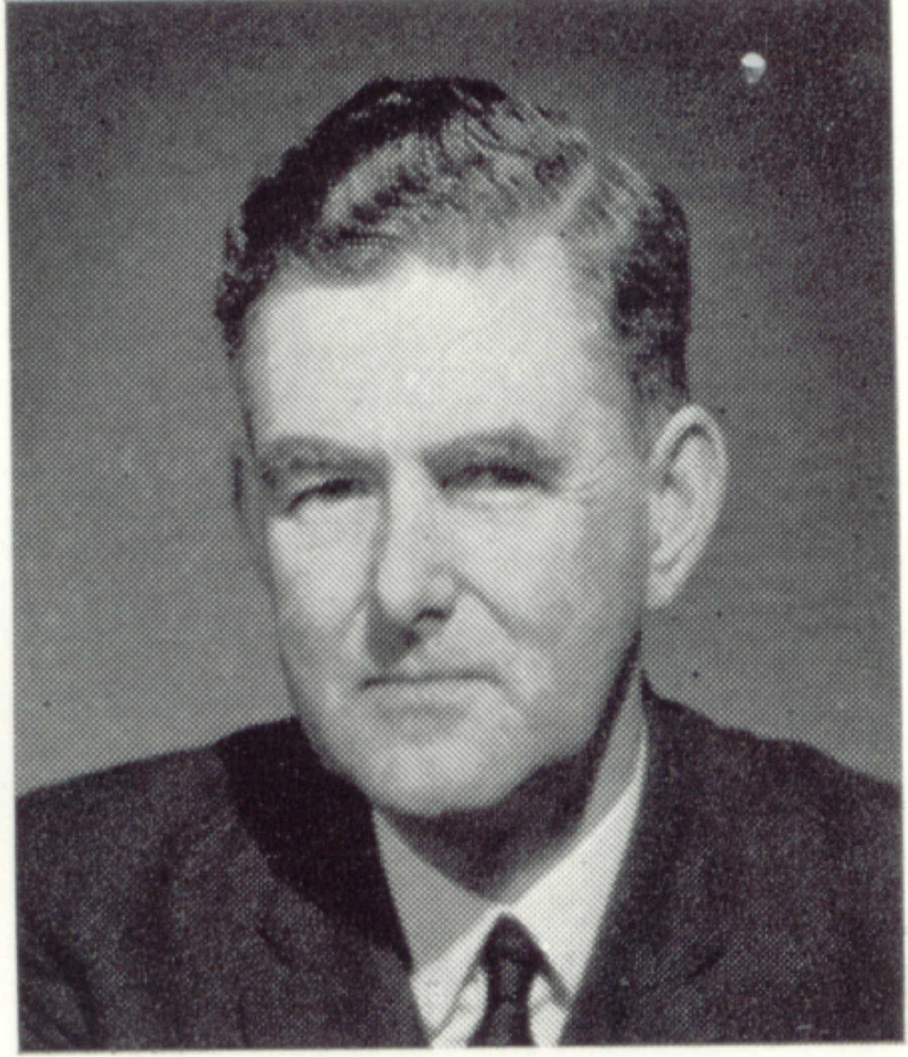


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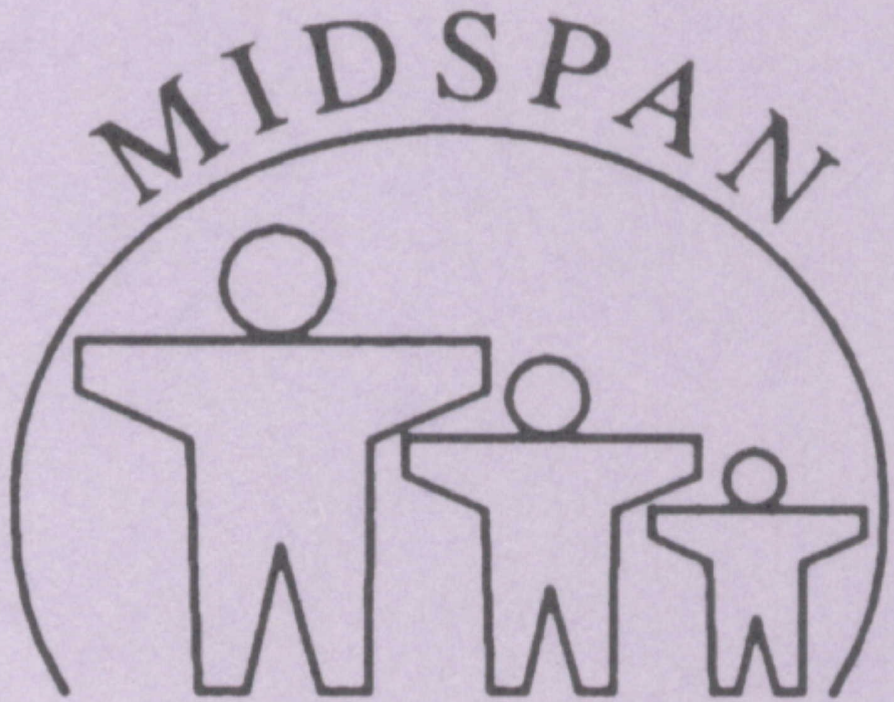
HIGHLANDS & ISLANDS


MIDSPAN