Cohort Profile

Cohort Profile: The Manitoba Follow-up Study (MFUS)

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†Dr FAL Mathewson, 1905–94.

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Abstract

The Manitoba Follow-up Study (MFUS) is Canada’s longest running study of cardiovascular disease and ageing. The MFUS cohort consists of 3983 men recruited from the Royal Canadian Air Force at the end of World War II. At entry to the study, 1 July 1948, their mean age was 31 years, with 90% between ages 20 and 39 years. All study members were free of clinical evidence of ischaemic heart disease. The protocol of MFUS was to obtain routine medical examinations from these men at regular intervals over time. The research goal of the study was to examine the role that any abnormalities detected on routine electrocardiograms from apparently healthy men might play in the prediction of subsequent diagnoses of cardiovascular disease. Over the course of 65 years, about 35% of the cohort has documented evidence of ischaemic heart disease. The research focus was expanded in 1996 to explore the roles of physical, mental and social functioning in support of healthy and successful ageing. On 1 July 2013, 429 original cohort members were alive with a mean age of 92 years. Collaborative research with others outside the in-house team is welcomed.

Key Messages

• The natural history of electrocardiographic abnormalities of conduction and rhythm in otherwise healthy men showed some abnormalities, such as left bundle branch block, ventricular premature beats and atrial fibrillation, to be strongly associated with manifestations of subsequent cardiovascular and cerebrovascular disease.

• There is strong evidence for tracking of cardiovascular risk factors of blood pressure and body build from youth to middle age in adult men.
Why was the cohort set up?
During World War II, Dr FAL Mathewson was responsible for the initial physical examination of approximately 7000 male recruits to evaluate their fitness for aircrew training in the Royal Canadian Air Force (RCAF). These examinations included physical measurement of height, body weight, blood pressure, medical history of past illnesses including childhood diseases and the recording of a resting electrocardiogram. During the war years, the value of these electrocardiograms came up for discussion on a few occasions where Dr Mathewson’s colleagues stressed the importance of setting up a long-term study to determine their clinical significance. Thus it was during the years of World War II that the seed was planted for the Manitoba Follow-up Study (MFUS). Because the cohort consisted of military personnel and veterans, the Canadian Defence Research Board and the Royal Canadian Air Force provided the staffing and resources needed to initiate MFUS.

As the study proceeded, its aim was clearly expressed by Dr Mathewson: ‘Because the suspicion of heart disease, particularly coronary artery disease, may have a far-reaching effect upon the individual, it is important to identify beyond any reasonable doubt the clinical significance of those variants that appear in the electrocardiograms of apparently healthy people’.4

Who is in the cohort?
Contact with the post-war survivors who had recruitment electrocardiograms was sought between 1946 and 1948, and each man was invited to take part in a longitudinal study of cardiovascular disease. A small group of 124 licensed pilots outside the RCAF were also enrolled at the request of the Department of Transport. A cohort of 3983 young men was sealed on 1 July 1948 and MFUS began. Unfortunately, no records were retained to determine how many of the 7000 original recruits survived the War, how many and who were able to be located and invited nor how many refused to participate. Furthermore, the process of signed, informed consent was not required for study participation in 1948. However, it has been acknowledged by the Human Research Ethics Board of the University of Manitoba that the continued response from MFUS members to surveys and requests for medical examinations can be seen as consent to participate in the study.

At entry, the mean age of the men in the cohort was 31 years, with three-quarters between 25 and 34 years of age. All men were free of clinical evidence of ischaemic heart disease. Baseline systolic and diastolic blood pressure and body mass index (mean ± standard deviation) were 121 ± 10 mmHg, 76 ± 8 mmHg and 23.8 ± 2.7 kg/m², respectively.

Approximately half of the cohort members (~2000) remained involved with aviation for a period of time after the War, and about half of those (~1000) were career pilots. The other half returned to school or began new or renewed civilian occupations. Occupations have ranged from ‘unemployed labourer’ to ‘chairman of the board’.

On 1 July 2013 there remained 429 study members now at a mean age of 92 years, 91% living in Canada with a geographical distribution similar to that of our national older adult population.

How often have they been followed up?
Study protocol evolved with the ageing of the cohort. Initially study members were contacted at 5-year intervals, then 3-year intervals, every year, twice a year and now three times each year. The medical data collected by calendar periods between 1948 and 2013 are described in Table 1. Table 2 describes mailed surveys sent to the members.

Follow-up between 1948 and 1963. During the first 15 years of the study, routine medical examinations including measurement of body weight, blood pressure and a resting electrocardiogram were requested from study members at 5-year intervals, with mailed requests staggered to balance staff workload. Approximately 800 men, one-fifth of the cohort, were contacted each year.

Follow-up between 1963 and 1978. As the frequency of incident clinical events increased with the age of the cohort, the frequency of routine examination requests increased to every 3 years between 1964 and 1978.
A lifestyle survey to obtain information on smoking, occupation and family history of disease was sent in 1974.

Follow-up between 1978 and 1996. Routine requests for physical examinations with an electrocardiogram continued at 3-year intervals. In 1978, a one-page Annual Contact Questionnaire (ACQ) was initiated to document self-rated health, new health events, physician visits and hospital admissions during the preceding year. The ACQ also requested signed authorization to contact the member’s physician or hospital to obtain details of diagnoses and procedures. The ACQ aids in timely documentation of illness between routine requests for medical examinations. Hence, attempts were made to contact all study members annually and, each year, one-third received examination requests. A second lifestyle survey was administered in 1982.

Follow-up between 1996 and 2007. Requests for routine medical examinations were discontinued in 1996. Follow-up with physicians and hospitals for details of visits and admissions reported on the ACQ continues. In 1996 a quality of life survey, the Successful Aging Questionnaire (SAQ), was designed and administered to capture core information about living arrangements, activities of daily living, quality of life and a narrative definition of successful ageing. The SAQ was administered again in 2000, 2002 and annually each spring since 2004. Hence since 2004, at 6-month intervals study members have been contacted at least twice a year, via the ACQ in the autumn and the SAQ in the spring.

Follow-up between 2007 and 2013. In December 2007, and repeated each year since, a nutritional risk survey was sent to all community-dwelling members residing in Canada. Hence since 2007, most Canadian study members have been contacted at least three times a year, and others living outside Canada at least twice each year.

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Figure 1 represents the 65-year experience of the MFUS cohort, describing cumulative mortality and ischaemic heart disease morbidity. Ischaemic heart disease in our study has been defined as clinical evidence of myocardial infarction, angina pectoris or sudden cardiac death. As shown by the upper component of the stacked bar, all 3983 members of the study were alive and free of ischaemic heart disease in 1948. Many years of observation are necessary with a young cohort to accrue sufficient endpoints to support analysis of cardiovascular disease. In 1978, 30 years into the study, 614 men had documented evidence of ischaemic heart disease and 3241 men were alive. Approximately half of the original cohort was alive in 1996 when the first SAQ was administered, but over the next 10 years half of those men died.

Absent from Figure 1 is a block displaying the very few men who were ‘lost-to-follow up’, a major concern in many cohort studies. The success of the follow-up process has been a highlight for MFUS. After the first 20 years, in the annual letter to the members, it was noted that 1968 marked the second consecutive year where contact was established with all living members of the Study. Annual letters to the members describing research highlights have helped to reinforce the importance of their participation, and hence contribute to member retention. The ‘lost-list’ of 1983 contained only six names. After 50 years of follow-up to 1 July 1998, fewer than 3% of the cohort had been lost to follow-up. On 1 July 2013, the date of death was known for 3554 men. Among the 429 men under study after 65 years, only 73 men, fewer than 2% of the original
cohort, had not been contacted during the previous 3 years. There is no plan for MFUS to end. Our intent is to maintain uninterrupted contact with study members and their families to document events as the men approach their natural end of life. Such events will include transitions from the community to long-term care, final hospitalizations, new diagnoses and circumstances and causes of death.

What has been measured?
Examinations were performed by members’ own personal physicians. Our database of clinical diagnoses is not based on self-report from study members, but rather on direct correspondence with physicians and receipt of hospital discharge summaries. Study physicians and cardiologists have interpreted and coded clinical conditions and electrocardiographic abnormalities since the study’s inception. Over 300 clinical conditions, diagnoses and procedures are listed in the study’s codebook. Data obtained over time are described in Table 1.

Periodically, more extensive mailed questionnaires have been used to obtain additional information, retrospectively, on lifestyle, successful ageing/quality of life, perception of involvement with MFUS and nutritional risk. Details of core and additional annual components of each survey are described in Table 2.

The lifestyle surveys were conducted in 1974 and 1982. Because smoking status was not obtained at entry to the study, smoking histories via these questionnaires are not available for men who died before the surveys were conducted. A chart review for men who had died before 1982 was conducted to supplement data on smoking habits, where smoking was mentioned on clinical reports from physicians.

By 1996, the mean age of the ~2000 surviving members of the cohort was 76 years. There was growing debate among gerontologists about policy and planning implications regarding the ageing population. We became particularly interested in the roles of physical, mental and social functioning in attaining and sustaining a healthy and successful passage through later life. Hence, our research focus was expanded to explore quality of life, and more specifically successful ageing, in our study members. The SAQ has been repeated a dozen times, such that in addition to the medical information we continue to collect, we now have a longitudinal component to study successful ageing. The SAQ has maintained a core component including the full SF-36 survey and narrative responses to two questions: ‘What is your definition of successful ageing?’, and ‘Have you aged successfully?’ These narrative definitions of successful ageing have added to an evolving literature on the value of understanding the concept of successful ageing from a lay perspective.

In 2003 and again in 2010, a short survey was conducted asking about members’ perceptions of their participation with MFUS and comments concerning the current and future value of MFUS. Similar findings from both surveys showed that whereas about two-thirds thought their participation in MFUS had been valuable to their own health and well-being, close to 90% felt the study had been worthwhile to medical science. The overwhelming majority felt that MFUS should continue, as long as MFUS researchers believe it is worthwhile.

For older adults, nutritional challenges may lead to malnutrition which may in turn lead to serious consequences including death. A nutrition survey, initiated in 2007, has now been conducted seven times to provide a longitudinal profile of changing nutritional risk of community-dwelling older men.

What was found?
Research results have been presented at local, national and international conferences and have been published in peer-reviewed journals of cardiology, general medicine, epidemiology and gerontology. All publications and the

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Number alive at beginning of period</th>
<th>Age ± standard deviation</th>
<th>Person-years of observation</th>
<th>Medical examination results</th>
<th>Electrocardiograms received</th>
<th>Blood pressure/body weight readings</th>
<th>Clinical codes assigned</th>
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</thead>
<tbody>
<tr>
<td>Pre 1 July 1948</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5375</td>
<td>530</td>
<td>6517</td>
<td></td>
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<tr>
<td>1 July 1948 to 30 June 1963</td>
<td>3983</td>
<td>31.1 ± 6.1</td>
<td>58475</td>
<td>17467</td>
<td>24131</td>
<td>6537</td>
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<tr>
<td>1 July 1963 to 30 June 1978</td>
<td>3786</td>
<td>46.0 ± 5.9</td>
<td>53392</td>
<td>26127</td>
<td>27649</td>
<td>23675</td>
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<tr>
<td>1 July 1978 to 30 June 1993</td>
<td>3268</td>
<td>60.3 ± 5.2</td>
<td>42260</td>
<td>19774</td>
<td>23813</td>
<td>37366</td>
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<tr>
<td>1 July 1993 to 30 June 2003</td>
<td>2254</td>
<td>74.2 ± 4.2</td>
<td>17725</td>
<td>4062</td>
<td>5187</td>
<td>13334</td>
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<tr>
<td>1 July 2003 to 30 June 2013</td>
<td>1287</td>
<td>83.2 ± 3.4</td>
<td>7652</td>
<td>1292</td>
<td>1883</td>
<td>5275</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>–</td>
<td>–</td>
<td>179504</td>
<td>74097</td>
<td>99193</td>
<td>92704</td>
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</table>
Table 2. Survey data collected in the Manitoba Follow-up Study

<table>
<thead>
<tr>
<th>Name and year of survey</th>
<th>Number sent</th>
<th>Number returned</th>
<th>Core content of questionnaire</th>
<th>Additional components</th>
</tr>
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<tr>
<td>Lifestyle Survey (LIFE)</td>
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<tr>
<td>LIFE1974</td>
<td>3483</td>
<td>3297</td>
<td>Smoking, family history of disease</td>
<td>Occupation</td>
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<tr>
<td>LIFE1982</td>
<td>3103</td>
<td>2677</td>
<td>Physical activity, wartime experiences</td>
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<tr>
<td>Successful Aging Questionnaire (SAQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAQ1996</td>
<td>2055</td>
<td>1779</td>
<td>Core content of all SAQs includes:</td>
<td>Occupation and retirement</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Living arrangements</td>
<td>Diet and nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ability to perform basic and instrumental activities of daily living</td>
<td>What is ‘being old?’</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Self-rated health and rated life satisfaction</td>
<td>Body weight recall, long-term effects of WWII</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• SF-36 (Ware 1992)</td>
<td>Changes in diet, driver and pilot licences</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Narrative response to two questions:</td>
<td>Care giving, income adequacy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>‘What is your definition of successful ageing?’, and ‘Have you aged successfully?’</td>
<td>How has your definition of successful ageing changed</td>
</tr>
<tr>
<td>SAQ2000</td>
<td>1661</td>
<td>1347</td>
<td></td>
<td>Important items determining quality of life</td>
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<td>SAQ2002</td>
<td>1474</td>
<td>1202</td>
<td></td>
<td>Important items determining quality of life</td>
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<td>SAQ2004</td>
<td>1214</td>
<td>899</td>
<td></td>
<td>Diet and nutrition, memory</td>
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<tr>
<td>SAQ2005</td>
<td>1112</td>
<td>891</td>
<td></td>
<td>Psychological control</td>
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<tr>
<td>SAQ2006</td>
<td>1001</td>
<td>841</td>
<td></td>
<td>Psychological control</td>
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<td>SAQ2007</td>
<td>880</td>
<td>707</td>
<td></td>
<td>Advice for military personnel today</td>
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<td>SAQ2008</td>
<td>757</td>
<td>611</td>
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<td></td>
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<tr>
<td>SAQ2009</td>
<td>667</td>
<td>551</td>
<td></td>
<td></td>
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<tr>
<td>SAQ2010</td>
<td>581</td>
<td>480</td>
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<td></td>
</tr>
<tr>
<td>SAQ2011</td>
<td>467</td>
<td>378</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAQ2012</td>
<td>386</td>
<td>307</td>
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<td></td>
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<tr>
<td>SAQ2013</td>
<td>330</td>
<td>248</td>
<td></td>
<td></td>
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<tr>
<td>Long-term health survey (LTHS)</td>
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<td>LTHS2003</td>
<td>1362</td>
<td>829</td>
<td>Perception of value to self and society of participation in MFUS</td>
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<td>LTHS2010</td>
<td>566</td>
<td>398</td>
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<tr>
<td>Nutritional Risk (NUT)</td>
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<tr>
<td>NUT2007</td>
<td>693</td>
<td>553</td>
<td>Content includes two parts:</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>• Part A: SCREEEN II Survey (HH Keller, 2004) Includes 14 questions to determine a nutritional risk score</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Part B: living arrangements, height, weight, income adequacy for food, medications, self-rated-health, perceptions of healthiness of diet and importance of nutrition to healthy ageing</td>
<td></td>
</tr>
<tr>
<td>NUT2008</td>
<td>516</td>
<td>454</td>
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<tr>
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<td>284</td>
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<tr>
<td>NUT2012</td>
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<tr>
<td>NUT2013</td>
<td>235</td>
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more recent presentations are listed on our website at [www.mfus.ca].

Initial research reports focused on case reports and case series of electrocardiographic findings. The first peer-reviewed manuscript was published in 1952, describing the experience of 57 men who had a P-R interval exceeding 0.20 s on their initial electrocardiograms at entry to the study. Through the early 1960s the first major reporting of the electrocardiographic abnormalities noted in conduction and rhythm were published in two companion papers; one report based on the whole cohort, and one based on the precursors among the 32 men documented with myocardial disease during the first 10 years of follow-up. The first general description of morbidity and mortality was undertaken after 15 years, after 143 men had developed coronary heart disease and 210 deaths had been documented. Body weight and blood pressure profiles were linked to these outcomes with descriptive statistical techniques. A gradient for increased risk of coronary heart disease was found with blood pressure, but not with body weight or heart rate. Men with non-specific ST–T wave changes were also shown to have an increased risk of developing coronary heart disease. Analyses conducted in the mid 1960s represented a major undertaking supported by actuarial scientists and the mainframe computer resources of the Great West Life Assurance Company in Winnipeg, MB.

In the 1970s, paper-based records of blood pressures and body weights, electrocardiograms, clinical diagnoses and mortality details were transcribed, coded and transferred to electronic data files stored on magnetic tape on the University of Manitoba Computer Centre’s mainframe computer. The first longitudinal analysis of blood pressure patterns described 26% of the cohort as having multiple readings beyond 140/90 over a 20-year period. This new in-house opportunity for analyses allowed MFUS researchers to address objectives and hypotheses pertaining to the natural history of electrocardiographic abnormalities and the relationship of body weight and blood pressure profiles to cardiovascular disease and cerebrovascular disease morbidity and mortality into the mid 1980s. The role of overweight as a risk factor for ischaemic heart disease was controversial in the early 1970s. Our analyses showed body mass index to have a stronger association with subsequent ischaemic heart disease in younger, rather than older men, and that the relationship was most strongly associated with sudden cardiac death. Productivity was summarized in 1987 in an article that described the first 35 years of MFUS research.

The 1990s heralded a new era for medical researchers with ever-increasing computing power, desktop computers, advances in biostatistical modelling and analytic software developments. More sophisticated longitudinal data analyses and exploration of chronic disease risk factors were published. Strong evidence for tracking of blood pressure and body mass index, i.e. the tendency for an individual to maintain his position relative to others, in the distribution of repeated measurements over time, was reported. Such a phenomenon for blood pressure is important, since men at highest risk for hypertension could be identified at younger ages, supporting strategies targeting early intervention. The effects of ageing on cardiovascular risk factors and the implication of ageing on the relationship between blood pressure and body build on subsequent ischaemic heart disease were reported. The adjusted relative risk associated with blood pressure and smoking for subsequent ischaemic heart disease were shown to decline with age, such that after age 65 years these risk factors were of little importance for the prediction of incident ischaemic heart disease.

The MFUS research focus was expanded in 1996 to include the study of successful ageing and in 2007 to include assessment of nutritional risk, resulting in the development of new longitudinal databases that complement the ongoing clinical records of the study. We approach the study of successful ageing from the perspective of the individual, and his ‘lay definition’ of successful ageing. Our repeated surveys with the SAQ described in Table 2 now include more than 10 000 narrative definitions of successful ageing. We have recently described 86 themes from these definitions, and have analysed the trends in these themes over a 10-year time frame, reporting that many themes maintain a constant prevalence over time, whereas others decline in prevalence with age. We have linked themes of successful aging to concepts of perceived psychological control and found that contrary to previous research, men prefer to retain control over everyday life well into advanced old age. Nutrition of older adults, particularly older community-dwelling men, remains an understudied topic. Student projects involving analysis of our nutrition surveys have shown a strong association between increasing frequency of food group consumption and perceptions of better overall self-rated health and life satisfaction, that 5-year change in food group consumption is related to better mental and physical functioning and that nutritional risk scores are strongly related to 5-year survival.

What are the main strengths and weaknesses?

This study is called the ‘Manitoba Follow-up Study’ not because the participants were from Manitoba, but rather because the study has been housed at the University
of Manitoba, in the Faculty of Medicine, stable and uninterrupted since its inception.

During the 65-year history of MFUS there have been three directors: FAL Mathewson, from 1948 to 1988; TE Cuddy from 1988 to 2001; and RB Tate since 2001. MFUS was the brainchild and was nurtured under the direction of Dr Mathewson. His passion for MFUS was infectious and has been a key determinant of the dedication of the research and support staff. A great strength in support of the longevity of MFUS has been the rapport established between the team of researchers and the study members. There is documented interest from the study members, our research team and our peers to see the study ‘to its natural end’. Indeed, a few study members have volunteered to be the last man!

A main strength of this study has been the completeness of the data collection; however, a limitation lies with the absence of systematic collection of blood and consequently no lipid profiles or genetic analysis is possible. MFUS is a study of men only. Hence, our results may not be generalizable to women. The generalizability of our results to ethnicities beyond the Caucasian population is cautioned.

MFUS is a prospective study of men’s lives. Studies of older men’s lives beyond 90 years of age are very rare. The ongoing opportunity to prospectively collect information, directly from the study members to the end of life, will support the development of future research hypotheses.

How was it funded?

The funding history of any 65-year study is likely an interesting story to tell, at least to other researchers. The early years of MFUS, under Dr Mathewson’s direction, were supported by the military (RCAF), the Canadian Research Council, the Defense Research Board, the Canadian Life Assurance Officers Association, the National Health Research Development Program (NHRDP, precursor of Canadian Institutes of Health Research) and numerous smaller foundations. In 1983, a site review committee from NHRDP concluded that enough data had been collected and that the study should wind down. The study members said ‘no’ and banded together to form MFUS-2000 with a pledge to finance the follow-up component of MFUS to the year 2000. For the following 17 years, and to some extent continuing today, many MFUS members would complete their annual contact questionnaire, write a personal cheque for $10, $50 or $100, and send both to us. From 1983 to 2000, it is estimated that 75% of our annual budgets were covered by study member donations. Currently, about $10,000 is still received annually from study members or from family members of deceased members. Since 2001, we have been successful in securing over 1.2 million dollars in peer-reviewed research funding to support MFUS, primarily from the Manitoba Health Research Council and the Canadian Institutes of Health Research.

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

The wealth of data already collected, the advanced age of the men and the size of this surviving cohort support opportunities for unique collaborations spanning numerous disciplines. The current interests of the in-house team span four areas: the study of successful ageing as a dynamic process over time; the development and application of methodologies for longitudinal data analysis; the exploration of the link between successful ageing and perceptions of psychological control; and the study of aspects of healthy nutrition and nutritional risk for older community-dwelling men. At present, use of data is confined to University of Manitoba office space. Anonymized files have been made available for University of Manitoba researchers at no cost. Random samples of MFUS records with selected variables have been made available to students and instructors for teaching purposes. We are open to discussion of any potential new collaboration. If interested, visit our website [www.mfus.ca] or contact the director at [Robert.Tate@med.umanitoba.ca].

Acknowledgements

The authors acknowledge the ongoing interest and contributions of the 3983 members of the MFUS cohort. Our most recent peer-reviewed operating grants were received from the Canadian Institutes of Health Research and the Manitoba Health Research Council (CIHR-MHRC-06719). We further gratefully acknowledge financial donations from MFUS members and their families.

Conflict of interest: None declared.

The reference list is available as a chronological listing of MFUS peer-reviewed publications in the Appendix

Appendix

5. Mathewson FAL, Varnam GS. Abnormal electrocardiograms in apparently healthy people. Part II. The electrocardiogram in the
51. Swift AU, Tate RB. Themes from older men’s lay definitions of successful aging as indicators of primary and secondary control beliefs over time: The Manitoba Follow-up Study. *J Aging Stud* 2013;27:410–18.