Cohort Profile: The Fremantle Diabetes Study (FDS)

Timothy M. E. Davis, David G. Bruce, Wendy A. Davis

School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia

Corresponding author: Professor T.M.E. Davis, University of Western Australia, School of Medicine and Pharmacology, Fremantle Hospital, PO Box 480, Fremantle, Western Australia 6959, Australia

Summary

The first phase (Phase I) of the Fremantle Diabetes Study (FDS) was set up as a detailed prospective observational cohort study to address the nature of diabetes care, control, complications and cost in a postcode-defined urban Australian setting with a particular emphasis on migrant and indigenous groups within the multi-ethnic Fremantle community. Of 2,258 potential subjects identified during registration between 1993 and 1996, 1,426 (63%) were recruited. Detailed annual assessments were carried out until 2001 but collection of morbidity and mortality data continues through health service linkages. In Phase II, 1,732 subjects were recruited, comprising 1,668 of 4,811 diabetic residents (34.7%) identified in the same catchment area between 2008 and 2011 plus 64 Phase I subjects who resided outside the study area. Phase II subjects were recruited to bi-ennial assessments complemented by alternate-year mailed-out questionnaires as well as the same external health service database linkage as Phase I. Phase I has produced a range of published data relevant to the epidemiology, management, outcome and costs of diabetes. Phase II will continue this theme but involves enhanced data collection and a wider potential range of specific research questions that can be addressed through interrogation of longitudinal observational data.

Key messages

Amongst a range of outcomes, the Fremantle Diabetes Study has found that

• relative to the majority Anglo-Celt ethnic group, patients of Southern European migrant stock have a high prevalence of type 2 diabetes and progress more rapidly to insulin therapy, and that Australian Aborigines with diabetes have worse glycaemic control and a poor prognosis

• fibrates are protective against peripheral neuropathy and that elderly males with type 2 diabetes benefit from low-dose aspirin in a primary prevention setting

• diabetes protects against abdominal aortic aneurysms but that peripheral vascular disease has an ominous prognosis in type 2 diabetes

• diabetes and, in particular, poor glycaemic control contribute to lung damage, while peripheral vascular disease and cerebrovascular disease are associated with dementia and depression, respectively, in type 2 patients

• the costs of diabetes in Australia are likely to quadruple over the next 40 years

Why was the cohort set up?

When the Fremantle Diabetes Study (FDS) Phase I was conceived in 1991 by its Chief Investigator (TMED), there were few published longitudinal community-based diabetes natural history studies. Population studies such as Framingham (**1**) in the US and Busselton (**2**) in Australia contained relatively small sub-groups from which limited additional diabetes-specific information was collected. The United Kingdom Prospective Diabetes Study (UKPDS) had recruited >5,000 newly-diagnosed type 2 subjects aged 25-65 years but the sample, although relatively large, was not community-based, the diagnosis of diabetes was based on a low fasting plasma glucose concentration (>6 mmol/L), and the study was interventional with outcomes presented in 1998 (**3**). There were also Australia-specific aspects of diabetes that had not been characterised in detail, especially the disproportionately large number of patients from a migrant (especially Southern European) background (**4**) and the important question of diabetes in indigenous groups (**5**).

The aim of FDS Phase I was, therefore, to identify from all potential sources, and collect detailed prospective data from, known diabetic patients in a stable multi-ethnic urban Australian population to examine clinically-relevant aspects of diabetes including clinical management, metabolic control, complications and cost. Based on the amount of available seeding funding from the Raine Foundation, University of Western Australia (WA) and respecting a reasonable patient time commitment and throughput, it was decided to attempt to recruit all consenting patients from the Fremantle Hospital (FH) primary catchment area, a postcode-defined population of approximately 120,000 living in and around the port of Fremantle in WA. A three-year registration period between 1993 and 1996 was followed by yearly reviews of the FDS Phase I cohort until 2001 (a minimum follow-up of 5 years) by which time more than half of the patients had died or withdrawn, although acquisition of

hospitalizations, cancer registrations and deaths through the WA Data Linkage System (WADLS) (**6**) has continued since.

During and after the active data collection in Phase I, the results of a number of studies were published that provided important data relating to diabetes epidemiology and management. The Australian Diabetes, Obesity, and Lifestyle (AusDiab) Study (**7**) showed that the prevalence of diabetes had increased at rates of 0.15%/year in males and 0.18%/year in females in individuals aged ≥25 years during the 19 years since the first Australian estimate from the Busselton survey in 1981 (**2**), while the incidence of type 1 diabetes in Australia was also increasing (**8**). A contributor to this increased prevalence was the lowering of the threshold fasting plasma glucose for diagnosis of diabetes from 7.8 mmol/L to 7.0 mmol/L by the World Health Organisation in 1999 (**9**).

In relation to management, results of the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes were first presented in 1993 and confirmed the benefits of tight glycaemic control in the prevention of microvascular disease (**10**). Parallel findings for type 2 diabetes from the UKPDS followed in 1998 (**3, 11**) but the UKPDS also highlighted the vascular benefits of intensive management of hypertension (**12**). Other landmark non-glycaemic intervention trials such as the Heart Outcomes Prevention Evaluation (HOPE and MICRO-HOPE) (**13**), the Heart Protection Study (**14**) and the Fenofibrate Intervention and Event Lowering in Diabetes Study (**15**) provided further evidence of the benefits of individual intensive vascular risk factor management in type 2 diabetes. The Steno-2 Study extended these findings in a multifactorial intervention that reduced both micro- and macrovascular disease (**16**). In addition, the 33% 2-year mortality rate in conventionally treated diabetic patients after myocardial infarction in the Diabetes Mellitus, Insulin Glucose Infusion in

Acute Myocardial Infarction (DIGAMI) Study carried out in the early 1990s (**17**) had fallen to 19% in similar patients in the more recent DIGAMI-2 (**18**) in the presence of increased use of aspirin, beta-blockers, ACEI and especially statin therapy. These studies were likely to have influenced changes in management of Australian diabetic patients during and after the active data collection in Phase I.

Although findings from Phase I had contributed to an understanding of the natural history of diabetes, the changes in diabetes epidemiology and management justified a Phase II which duplicated and extended data collection. Funding for this new study was obtained from the National Health and Medical Research Council of Australia and it started in the first part of 2008, some 15 years after the first patient was recruited to Phase I. The Phase II baseline cohort was recruited over a three-year period from the same catchment area using similar methods of ascertainment as Phase I. Longitudinal follow-up data collection is continuing at present.

Who is in the cohort?

The samples for Phase I and II have been drawn from the same geographical area. From Australian Bureau of Statistics data (**19**), there were 120,000 people in the postcode-defined catchment area at the start of Phase I in 1993 and 153,000 in 2008 at the start of Phase II. In addition to a 28% increase in the population during the 15 years between Phases, the demography and ethnic mix have changed. For example, the percentage born in Southern Europe has fallen from 7.4% to 2.5%, and the mean age has increased with those aged ≥50 years comprising 30.7% compared with 25.6% in 1993.

In Phase I, diabetic patients resident in the study catchment area were identified from FH

clinic and inpatient lists, local physician referrals, allied health facilities, pharmacies, opticians, advertising in local media and word of mouth. Of 2,258 potential subjects identified during registration between 1993 and 1996, 1,426 (63%) were recruited (**20, 21**). This compares favourably with the AusDiab Study which recruited 41% of randomly-selected households and obtained biomedical data from 56% of identified individuals within them (**7**). A range of baseline and outcome data was also collected from the 832 patients who were identified but not recruited to provide an objective assessment of the representative nature of the sample. Eligible patients who declined participation were a mean of 1.4 years older than participants, but their country of birth, sex distribution, and the distributions of diabetes types and treatment modalities, were similar (**20, 21**).

For Phase II, recruitment strategies were the same as those used in Phase I except that third-party mail-outs of potentially eligible patients were arranged through the Australian National Diabetes Supply Scheme and National Diabetes Register. A consort diagram that summarises recruitment is shown in Figure 1. There were 4,979 diabetic patients identified between 2008 and 2011, including 796 original Phase I surviving participants of whom 168 had moved out of the study area but from whom long-term follow-up data were being sought. A total of 1,732 (34.8%) were recruited to Phase II (including 64 non-resident Phase I subjects), a lower rate than Phase I but still higher than AusDiab (**7**). Exclusion of the out-of-area participants left 4,811 identified and residing within the study area with 1,668 (34.7%) of these recruited.

As in Phase I, data are being collected to characterize as many non-recruited patients as possible from all possible sources (see Table 1). Phase II non-recruited subjects were a mean of 1.2 years younger than participants at the start of recruitment but their sex distribution was

similar with just over 50% males. Available preliminary data for other variables including ethnicity do not show marked differences.

How often have they been followed up?

In Phase I, baseline and subsequent annual assessments were performed until death, withdrawal, relocation out of the study area or the close-out of individual patient data collection in 2001 (see Table 2). The WADLS was established in 1995 to connect all available health and related information for the WA population (**6**). The Fremantle Diabetes Study has been linked with the WADLS since 2001 and continues to receive regular data updates. The latest regular update was in early 2011, providing up to 17 years of follow-up of our Phase I cohort. Data collections linked by WADLS include core datasets comprising the Hospital Morbidity Data Collection (HMDC; since 1970), Emergency Department Data Collection (since 2002), Western Australian Cancer Registry (since 1982), and the Death Register (since 1969). Linkage has also been possible to Silver Chain (**22**) (one of the largest providers of community and health services to the WA community) and St John Ambulance (**23**) (the main ambulance provider in WA) in collaboration with their respective data custodians but facilitated by the WADLS. The Metropolitan Cemeteries Board (**24**) database and individual hospital case-notes have also complemented and validated linkage data.

At the beginning of Phase II recruitment in mid-February 2008, 603 (42.3%) of the original Phase I cohort had died and 27 were lost to follow-up (18 had definitely/probably moved overseas or interstate, whilst the whereabouts of 9 was unknown). By the end of Phase II recruitment at end-June 2011, a further 124 had died, 106 of whom were unable to be recruited to Phase II out of the remaining 406 Phase I patients (see Table 2). In summary, <2% of the original cohort is no longer providing data for analyses. Table 1 compares the

characteristics of Phase I participants who i) were recruited to Phase II, ii) who were alive at the start of Phase II recruitment and had not been lost to follow-up but who were not recruited, with iii) those who either died before Phase II started or were lost to follow-up before Phase I.

In Phase II, baseline and subsequent biennial detailed assessments will be performed until death or withdrawal, but questionnaires are being sent out every second year to gather data including those relating to changes in management, and the development of complications and co-morbidities, to complement full in-person data collection. In contrast to Phase I, relocation out of the study area will not be a criterion for cessation of active data collection. As the recruitment period for Phase II only recently closed, there has been insufficient time for an assessment of attrition in this cohort.

What has been measured?

The data collected at baseline and at each subsequent visit (annually for Phase I and biennially for Phase II) are summarized in Table 3. Modified questionnaires are sent out to Phase II participants in intervening years based on the self-reported data collected in person. In both phases, patients have attended after a >10-hour overnight fast with venous blood and spot morning urine specimens collected, and serum and plasma prepared from centrifuged blood. Routine care analytes are assayed the same day in a single nationally-accredited biochemistry laboratory. Either the same assay methodology has been used for both Phases or calibration equations are applied when assays change.

What has it found? Key findings and publications

There have been over 60 peer-reviewed publications reporting Phase I data (see

(http://www.medpharm.uwa.edu.au/research/fremantle_diabetes_study). The broad research themes covered by Phase I have been:

i) Epidemiology. These reports have ranged from the identification of a low prevalence of latent autoimmune diabetes of adults (LADA) in a multi-ethnic setting (**21**) and a poor outcome in type 2 indigenous patients (**25**), to an assessment of the nature of type 2 diabetes in young (**26**) and elderly (**20**) Australians. Phase I also showed that people from Southern European migrant stock have a high prevalence of diabetes and progress more rapidly to insulin therapy than other ethnic groups (**27**) but do not die at a younger age as a result (**28**).

ii) Clinical management. Contributions in this area have ranged from data suggesting that fibrates are protective against peripheral neuropathy (**29**), that elderly males with type 2 diabetes would benefit from low-dose aspirin in a primary prevention setting (**30**), and that renin-angiotensin system blocking drugs have equivalent effect on albuminuria in community-based patients to those reported in clinical trials (**31**), to the development of an Australian diabetes cardiovascular risk calculator (**32**) and a diabetes-specific hand-held medical record (**33**). Our data have questioned the value of self-monitoring of blood glucose (SMBG) in non-insulin treated patients with type 2 diabetes (**34**) and have contributed to the development of the International Diabetes Federation SMBG guidelines (**35**).

iii) Acute and chronic complications. In relation to acute complications, Phase I data have shown that, in parallel with large-scale glycaemic intervention studies (**36**), severe hypoglycemia is paradoxically associated with a higher HbA_{1c} in type 2 diabetes (**37**), while metformin-associated lactic acidosis is rare (**38**). Regarding chronic complications, we found that diabetes protects against abdominal aortic aneurysms (**39**) but that peripheral arterial disease (PAD) has an ominous prognosis in type 2 diabetes (**40**). The presence of carotid bruit, an easily detectable sign, proved to be a strong predictor of stroke amongst type 2

patients (**41**), while serum HDL-cholesterol was the strongest modifiable predictor of first stroke in type 1 subjects (**42**). Analyses have also confirmed that silent myocardial infarction is common in diabetes but that the prognosis in such patients is better than in those with symptomatic presentations (**43**).

iv) Unconventional complications. Phase I provided some of the first data linking diabetes and, in particular, poor glycaemic control to lung damage (**44**) and added to data implicating type 1 diabetes as a risk factor for osteoporosis (**45**). Diabetic patients with PAD are particularly susceptible to cognitive decline and dementia (**46**) while a history of cerebrovascular disease is a strong predictor of depression in type 2 patients (**47**). Diabetes is a risk factor for hepatobiliary disease and associated mortality (**48**), but the contribution of fatty liver appears to have been overestimated.

v) Health-economic implications. Phase I data have shown that the costs of diabetes in Australia could quadruple over the next 40 years if current trends continue (**49**), with a substantial contribution from medications to treat non-glycaemic cardiovascular risk factors (**50**). However, even moderate weight loss (≥5% of initial body weight) confers important cost savings (**51**).

Phase I spawned the Fremantle Diabetes and Cognition Study which has produced a range of data including evidence that community-living older diabetic subjects have high rates of cognitive impairment, deficits in physical function and depressive symptomatology (**52**).

What are the main strengths and weaknesses?

The strengths of both Phases of the FDS are the inclusive and generally representative nature of the cohorts, the range and detail of data collection, and linkage to well established morbidity and mortality databases in WA and, in future, Australia as a whole. The design and

implementation of the FDS means that specific questions regarding the natural history of diabetes, its impact on the individual and its costs can be addressed with relative rigour. The main weakness was the proportion of patients who were not recruited or who withdrew despite repeated attempts to contact them and, if this was successful, to arrange assessments at a convenient time. The lower recruitment rate in Phase II vs Phase I reflected, in part, the institution of government-funded diabetes care plans through primary care in 1999 (**53**) that ensured availability of free or subsidized regular metabolic and complications screening. The FDS assessment was considered by some potential recruits and previous participants as a duplication of this service.

Specific limitations of Phase I, which arose partly because of the time when it was designed, have been addressed in Phase II, including i) employment of an Aboriginal health worker to facilitate recruitment and follow-up of indigenous patients (112 recruited to Phase II compared with only 18 in Phase I), ii) third-party mail-outs through national diabetes-related organisations that helped quantify the number of people in the catchment area with diabetes as well as facilitating recruitment, iii) pre-appointment posting of questionnaires to be completed in advance and thus reduce the time commitment (between 2 and 3.5 hours if data were collected), iv) institution of home assessments for patients unable to attend FH, and v) availability out-of-hours assessment timeslots for young, working patients.

The choices of sample size and range of data to be collected in a study such as FDS are restrained by financial and logistic considerations. Relatively subtle but clinically important effects of diabetes on outcomes may be missed if the sample size is too small. However, attrition from natural causes and patient withdrawal, such as that which occurred in Phase I, should be factored in to sample size selection. Patient recruitment and retention are dependent

on time commitment which can be reduced if processes are in place that allow patients to progress through varied assessments and procedures efficiently. Employing dedicated personnel to engage special groups (such as those from an indigenous background) is strongly recommended, as evidenced by an increase in Aboriginal participants from 1.3% of the cohort in Phase I to 6.5% in Phase II.

FDS data are observational and subject to inherent limitations. An example of this is when intervention effects are estimated. Nonetheless, there is little evidence that such estimates in well-conducted observational studies are consistently larger than, or qualitatively different from, those obtained in randomized controlled trials (RCTs) (**54**). RCTs remain the gold standard evidence base for management of complex conditions such as diabetes but observational studies can be useful or complementary where RCTs have incomplete coverage or are difficult. Examples include recruitment of the elderly or those with multiple complications, and when effects may be maximal over a long period of follow-up.

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

The data are held in a secure, confidential database which can only be accessed by members of the FDS team. The data custodian is the FDS biostatistician (WAD) who, with the Chief Investigator (TMED), is the main point of contact. The FDS has a dedicated website (http://www.medpharm.uwa.edu.au/research/fremantle_diabetes_study). Researchers with similar data who might want to share ideas or suggest collaborative projects should contact TMED or WAD.

Acknowledgements

We are grateful to FDS staff for help with collecting and recording clinical information. We thank the Biochemistry Department at Fremantle Hospital and Health Service for performing laboratory tests, and the Diabetic Education, Podiatry and Dietetic Departments for assistance with recruitment of patients. The WADLS is acknowledged for provision of morbidity and mortality data. The Fremantle Diabetes Study was funded by the Raine Foundation, University of Western Australia (Phase I) and the National Health and Medical Research Council (NHMRC) of Australia. TMED is supported by a NHMRC Practitioner Fellowship.

Conflict of Interest

None declared.

References

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;**241**: 2035-8.

2. Glatthaar C, Welborn TA, Stenhouse NS, Garcia-Webb P. Diabetes and impaired glucose tolerance. A prevalence estimate based on the Busselton 1981 survey. *Med J Aust* 1985;**143**: 436-40.

3. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**: 837-53.

4. Welborn TA, Knuiman MW, Bartholomew HC, Whittall DE. 1989-90 National Health Survey: prevalence of self-reported diabetes in Australia. *Med J Aust* 1995;**163**: 129-32.

5. O'Dea K. Diabetes in Australian aborigines: impact of the western diet and life style. *J Intern Med* 1992;**232**: 103-17.

6. Holman CD, Bass AJ, Rouse IL, Hobbs MST. Population-based linkage of health records in WA: development of a health services research linked database. *Aust NZ J Publ Hth* 1999;**23**: 453-9.

7. Dunstan DW, Zimmet PZ, Welborn TA, et al. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) - methods and response rates. *Diabetes Res Clin Pract* 2002;**57**: 119-29.

8. Taplin CE, Craig ME, Lloyd M, et al. The rising incidence of childhood type 1 diabetes in New South Wales, 1990-2002. *Med J Aust* 2005;**183**: 243-6.

9. World Health Organization DoNDS. *Report of a WHO Consultation, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1 Diagnosis and classification of diabetes mellitus* Geneva: World Health Organization; 1999.

10. DCCT Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;**329**: 977-86.

11. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**: 405-12.

12. UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;**317**: 703-13.

13. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;**355**: 253-9.

14. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;**361**: 2005-16.

15. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;**366**: 1849-61.

16. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;**348**: 383-93.

17. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 1997;**314**: 1512-5.

18. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;**26**: 650-61.

19. Australian Bureau of Statistics. *Population by Age and Sex, Australian States and Territories, Jun 2010*. 2010 [cited 2011 November]; Available from: http://www.abs.gov.au/Ausstats/abs@.nsf/mf/3201.0

20. Bruce DG, Davis WA, Davis TM. Glycemic control in older subjects with type 2 diabetes mellitus in the Fremantle Diabetes Study. *J Am Geriatr Soc* 2000;**48**: 1449-53.

21. Davis TM, Zimmet P, Davis WA, Bruce DG, Fida S, Mackay IR. Autoantibodies to glutamic acid decarboxylase in diabetic patients from a multi-ethnic Australian community: the Fremantle Diabetes Study. *Diabet Med* 2000;**17**: 667-74.

22. Silver Chain. *Silver Chain Nursing Association home page*. 2011 [cited 2011 November]; Available from: http://www.silverchain.org.au/

23. St John Ambulance Australia. *St John Ambulance home page*. 2011 [cited 2011 November]; Available from: http://www.stjohnchangelives.com.au/

24. Government of Western Australia. *Metropolitan Cemeteries Board home page*. 2011 [cited 2011 November]; Available from: http://www.mcb.wa.gov.au/ResearchAndGenealogy/Search.aspx

25. Davis TM, McAullay D, Davis WA, Bruce DG. Characteristics and outcome of type 2 diabetes in urban Aboriginal people: the Fremantle Diabetes Study. *Intern Med J* 2007;**37**: 59-63.

26. Sillars BA, Davis WA, Kamber N, Davis TM. The epidemiology and characteristics of type 2 diabetes in urban, community-based young people. *Intern Med J* 2010;**40**: 850-4.

27. Clifford RM, Davis WA, Cull CA, Bruce DG, Batty KT, Davis TM. Greater use of insulin by southern European compared with Anglo-Celt patients with type 2 diabetes: the Fremantle Diabetes Study. *Eur J Endocrinol* 2004;**151**: 579-86.

28. Davis WA, Chin E, Jee A, et al. Apolipoprotein E genotype and mortality in Southern European and Anglo-Celt patients with type 2 diabetes: the Fremantle Diabetes Study. *Eur J Endocrinol* 2010;**163**: 559-64.

29. Davis TM, Yeap BB, Davis WA, Bruce DG. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* 2008;**51**: 562-6.

30. Ong G, Davis TM, Davis WA. Aspirin is associated with reduced cardiovascular and all-cause mortality in type 2 diabetes in a primary prevention setting: the Fremantle Diabetes study. *Diabetes Care* 2010;**33**: 317-21.

31. Fegan PG, Davis WA, Kamber N, Sivakumar S, Beilby J, Davis TM. Renin-angiotensin-aldosterone system blockade and urinary albumin excretion in community-based patients with Type 2 diabetes: the Fremantle Diabetes Study. *Diabet Med* 2011;**28**: 849-55.

32. Davis WA, Knuiman MW, Davis TM. An Australian cardiovascular risk equation for type 2 diabetes: the Fremantle Diabetes Study. *Intern Med J* 2010;**40**: 286-92.

33. Davis TME, Bridgford A. A comprehensive patient-held record for diabetes (2): large-scale assessment of the Diabetes Databank by patients and health care workers. *Pract Diabetes Internat* 2001;**18**: 311-4.

34. Davis WA, Bruce DG, Davis TM. Does self-monitoring of blood glucose improve outcome in type 2 diabetes? The Fremantle Diabetes Study. *Diabetologia* 2007;**50**: 510-5.

35. International Diabetes Federation. *Guideline. Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes*. 2009 [cited 2011 November]; Available from: http://www.idf.org/webdata/docs/SMBG_EN2.pdf

36. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010;**340**: b5444.

37. Davis TM, Brown SG, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. *J Clin Endocrinol Metab* 2010;**95**: 2240-7.

38. Kamber N, Davis WA, Bruce DG, Davis TM. Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study. *Med J Aust* 2008;**188**: 446-9.

39. Mattes E, Davis TM, Yang D, Ridley D, Lund H, Norman PE. Prevalence of abdominal aortic aneurysms in men with diabetes. *Med J Aust* 1997;**166**: 630-3.

40. Norman PE, Davis WA, Bruce DG, Davis TM. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2006;**29**: 575-80.

41. Gillett M, Davis WA, Jackson D, Bruce DG, Davis TM. Prospective evaluation of carotid bruit as a predictor of first stroke in type 2 diabetes: the Fremantle Diabetes Study. *Stroke* 2003;**34**: 2145-51.

42. Davis TM, Bruce DG, Davis WA. Predictors of first stroke in Type 1 diabetes: The Fremantle Diabetes Study. *Diabet Med* 2005;**22**: 551-3.

43. Davis TM, Fortun P, Mulder J, Davis WA, Bruce DG. Silent myocardial infarction and its prognosis in a community-based cohort of Type 2 diabetic patients: the Fremantle Diabetes Study. *Diabetologia* 2004;**47**: 395-9.

44. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2004;**27**: 752-7.

45. Rakic V, Davis WA, Chubb SA, Islam FM, Prince RL, Davis TM. Bone mineral density and its determinants in diabetes: the Fremantle Diabetes Study. *Diabetologia* 2006;**49**: 863-71.

46. Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia* 2008;**51**: 241-8.

47. Bruce DG, Casey G, Davis WA, et al. Vascular depression in older people with diabetes. *Diabetologia* 2006;**49**: 2828-36.

48. Davis TME, Peters KE, Bruce DG, Davis WA. Prevalence, incidence and prognosis of hepatobiliary disease in community-based patients with type 2 diabetes: The Fremantle Diabetes Study. *J Clin Endocrinol Metab* 2012;**in press**.

49. Davis WA, Knuiman MW, Hendrie D, Davis TM. The obesity-driven rising costs of type 2 diabetes in Australia: projections from the Fremantle Diabetes Study. *Intern Med J* 2006;**36**: 155-61.

50. Davis WA, Knuiman MW, Hendrie D, Davis TM. Determinants of diabetes-attributable non-blood glucose-lowering medication costs in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2005;**28**: 329-36.

51. Davis WA, Bruce DG, Davis TM. Economic impact of moderate weight loss in patients with Type 2 diabetes: the Fremantle Diabetes Study. *Diabet Med* 2011;**28**: 1131-5.

52. Bruce DG, Casey GP, Grange V, et al. Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: the Fremantle Cognition in Diabetes Study. *Diabetes Res Clin Pract* 2003;**61**: 59-67.

53. Shortus TD, McKenzie SH, Kemp LA, Proudfoot JG, Harris MF. Multidisciplinary care plans for diabetes: how are they used? *Med J Aust* 2007;**187**: 78-81.

54. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000;**342**: 1878-86.

55. Ireland P, Jolley D, Giles G, et al. Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. *Asia Pacific J Clin Nutr* 1994;**3**: 19-31.

56. Lewis J, Milligan G, Hunt A. *NUTTAB95 Nutrient Data Table for Use in Australia*. Canberra: Australian Government Publishing Service; 1995.

57. Salmon J, Owen N, Crawford D, Bauman A, Sallis JF. Physical activity and sedentary behavior: a population-based study of barriers, enjoyment, and preference. *Health Psychol* 2003;**22**: 178-88.

58. Australian Institute of Health and Welfare. *The Active Australia Survey: A Guide and Manual for Implementation, Analysis and Reporting*. Canberra: Australian Institute of Health and Welfare; 2003.

59. Karlander SG, Alinder I, Hellstrom K. Knowledge of diabetes mellitus, diets and nutrition in diabetic patients. *Acta Med Scand* 1980;**207**: 483-8.

60. Brauer PM, McKeown-Eyssen GE, Jazmaji V, et al. Familial aggregation of diabetes and hypertension in a case-control study of colorectal neoplasia. *Am J Epidemiol* 2002;**156**: 702-13.

61. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;**131**: 485-91.

62. Rosser R, Kind P. A scale of valuations of states of illness: is there a social consensus? *Int J Epidemiol* 1978;**7**: 347-58.

63. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 1999;**8**: 79-91.

64. Jacobson AM, de Groot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. *Diabetes Care* 1994;**17**: 267-74.

65. McMillan CV, Honeyford RJ, Datta J, Madge NJ, Bradley C. The development of a new measure of quality of life for young people with diabetes mellitus: the ADDQoL-Teen. *Health Qual Life Outcomes* 2004;**2**: 61.

66. Australian Health Outcomes Collaboration. *SF-12® Health Survey (Version 1.0). Instrument review*. 2005 [cited 2011 November]; Available from: http://ahsri.uow.edu.au/ahoc/documents/sf12review.pdf

67. Burke WJ, Miller JP, Rubin EH, et al. Reliability of the Washington University Clinical Dementia Rating. *Arch Neurol* 1988;**45**: 31-2.

68. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;**16**: 606-13.

69. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;**9**: 179-86.

70. Davis WA, Norman PE, Bruce DG, Davis TM. Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* 2006;**49**: 2634-41.

71. Strain GW, Wang J, Gagner M, Pomp A, Inabnet WB, Heymsfield SB. Bioimpedance for severe obesity: comparing research methods for total body water and resting energy expenditure. *Obesity* 2008;**16**: 1953-6.

72. Ewing DJ. Testing for autonomic neuropathy. *Lancet* 1981;**1**: 224.

73. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994;**17**: 1281-9.

74. Meerwaldt R, Graaff R, Oomen PH, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia* 2004;**47**: 1324-30.

75. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005;**18**: 3S-10S.

Figure captions

Figure 1. Consort diagram showing patient recruitment for both phases of the FDS.

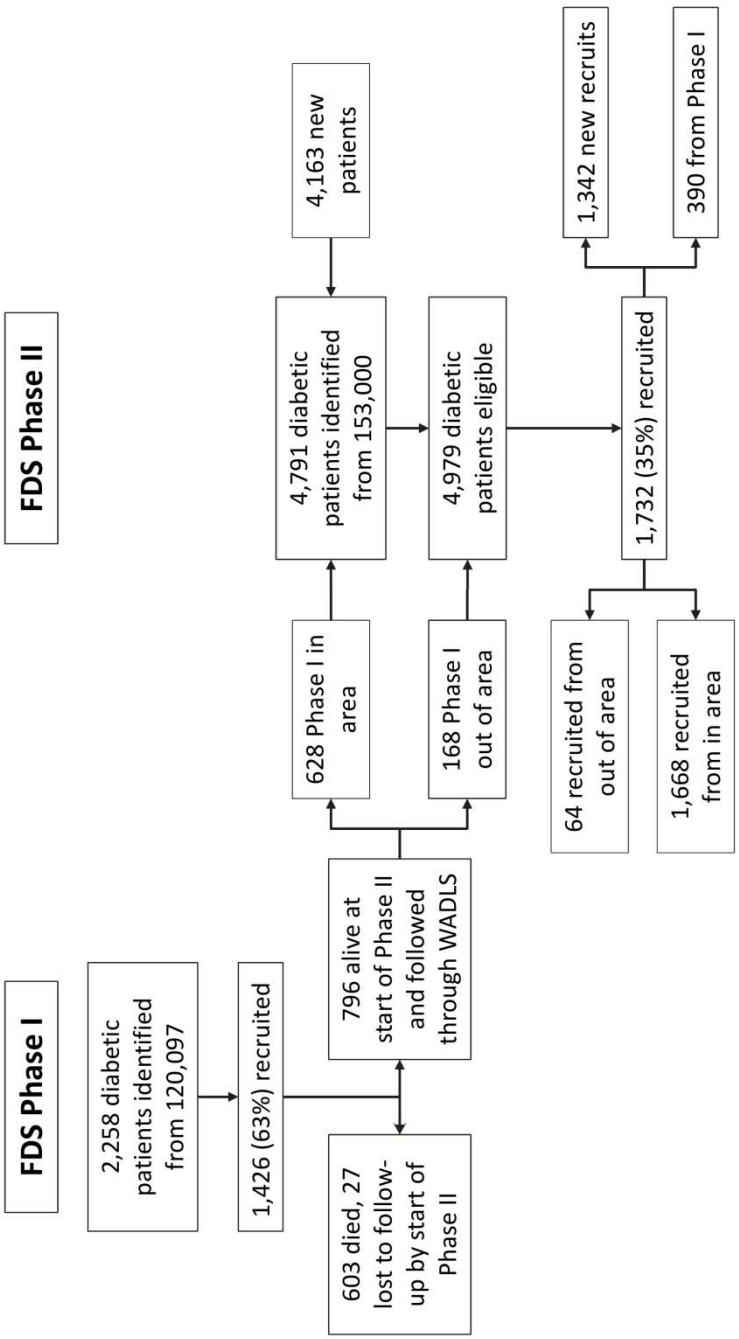

Table 1. Comparison of characteristics of diabetic residents recruited to and not recruited to FDS Phase II, including those who also participated in Phase I. Data are mean±SD or median [inter-quartile range].

		New recruits to Phase II	New non-recruits to Phase II	*P*-value#	Phase II recruits from Phase I	Phase II non-recruits from Phase I	Phase I recruits deceased/lost to follow-up before Phase II	*P*-value#
N		1,342	2,841		390	406	630	
Age† (years)		60.4±13.8	59.3±17.8	0.033	68.4±11.9	72.5±13.2***	82.3±11.0***, ###	<0.001
Sex (% male)		51.9	52.9	0.57	52.6	39.7***	54.3###	<0.001
Ethnic background† (%):	Anglo-Celt	53.2	49.4		64.9	62.8	64.3	0.66
	Southern European	11.1	19.7		16.9	20.0	17.5	
	Other European	6.9	10.7		8.2	6.9	9.2	
	Asian	4.1	6.9		4.1	3.7	2.1	
	Indigenous	8.0	5.4		1.0	1.2	1.6	
	Mixed/other	16.8	7.9		4.9	5.4	5.4	
Not fluent in English (%)		8.8	-		12.1	13.8	16.4	0.16
Educated beyond primary level (%)		89.2	-		82.9	73.9**	71.2***	<0.001
Diabetes type¶ (1/2/other; %)		6.6/91.4/2.0	3.8/95.9/0.3		12.8/86.9/0.3	9.1/90.6/0.2	6.0/93.5/0.5**	0.003
Diabetes duration‡ (years)		7.0 [2.9-13.3]	-		16.6 [14.3-20.3]	17.2 [14.6-21.5]	19.4 [15.7-26.4] ***, ###	<0.001
Deceased during Phase II recruitment (n(%))		34 (2.5)	295 (10.4)	<0.001	18 (4.6)	106 (26.1)	n/a	<0.001

#Pairwise comparisons (other than for variables with incomplete data) unadjusted for multiple comparisons: †Ethnic background for 1,425 newly-identified diabetic patients who were not recruited to Phase II was based on country of patient's birth only compared with self-selection, country of patient's birth, country of father's/mother's birth, and language spoken at home in Phase I; ¶Data are for 1,297 new non-recruits to Phase II; ‡Projected for those who died before Phase II started; *P<0.05, **P<0.01, ***P<0.001 (Phase II recruits as reference), #P<0.05, ##P<0.01, ###P<0.001 (Phase II non-recruits as reference)

Table 2. Longitudinal demographic data of FDS Phase I participants and reasons for loss to follow-up.

Annual review #	Phase 1	1	2	3	4	5	6	7	8	Phase 2
N (%)	baseline 1426 (100)	1131 (79.3)	956 (67.0)	828 (58.1)	694 (48.7)	579 (40.6)	410 (28.8)	225 (15.8)	35 (2.5)	baseline 390 (27.3)
Follow-up time (years)	0	1.1 [1.0, 1.2]	2.1 [2.0, 2.4]	3.2 [3.0, 3.5]	4.2 [4.1, 4.5]	5.3 [5.1, 5.6]	6.3 [6.2, 6.6]	7.3 [7.2, 7.5]	8.2 [8.0-8.3]	14.7 [14.0-15.4]
Age (years)	62.1± 13.3	63.3±12.3	64.1±11.9	64.9±11.6	65.8±11.2	66.5±10.9	67.2±10.1	69.5±9.0	74.8±5.7	69.7±11.8
Gender (% male)	49.6	51.1	51.9	52.8	53.6	55.1	54.1	52.4	54.3	52.6
Diabetes type (% 1/2/other)	8.9/90.7/0.4	8.1/91.5/0.4	8.1/91.5/0.4	8.2/91.5/0.2	7.9/91.8/0.3	7.9/91.7/0.3	6.6/92.9/0.5	4.9/94.7/0.4	2.9/97.1/0	13.3/86.4/0.3 †
Diabetes duration (years)	4.0 [1.0-10.0]	5.1 [2.1-11.0]	6.1 [3.1-11.1]	7.1 [4.2-11.8]	8.0 [5.2-12.4]	9.0 [6.3-13.2]	9.8 [7.4-13.7]	11.2 [8.3-14.8]	12.4 [9.7-17.9]	17.9 [15.6-21.7]
Marital status (% currently married/de facto relationship)	64.7	65.8	66.4	64.1	66.2	63.8	66.4	67.9	73.5	55.4
English ability (% non-fluent)	14.5	14.1	13.1	12.7	12.5	12.1	10.2	8.0	0	14.1
Educational attainment (% ≤ primary schooling)	24.8	24.5	22.8	23.0	22.5	21.6	19.7	19.1	22.9	19.3
Ethnic background (%):										‡
Anglo-Celt	64.0	65.2	65.3	65.7	67.3	68.6	70.2	76.0	80.0	64.9
Southern European	18.0	17.6	17.3	17.4	17.1	16.6	15.6	14.2	11.4	16.9
Other European	8.3	8.0	7.8	8.1	8.6	8.5	7.8	5.3	5.7	8.2
Asian	3.1	3.4	3.7	3.3	3.0	2.8	2.7	1.3	0	4.1
Mixed/other	5.3	5.0	5.2	5.0	3.7	3.5	3.4	3.1	2.9	4.9
ATSI	1.3	0.9	0.7	0.6	0.1	0.2	0.2	0	0	1.0
Reasons for loss to follow-up (n):										
Death# (165 (11.6%))		45	30	21	20	24	11	11	3	603+106
Moved out of area (124 (8.7%))		69	23	13	10	4	5	0	0	2††
Withdrew (421 (29.5%))		143	99	68	70	31	8	2	0	205
Unknown* (84 (5.9%))		38	6	6	9	10	12	3	0	n/a
Study closed** (632 (44.3%))		17	20	25	46	133	169	187	35	n/a
Total (1426)		312	178	133	155	202	205	203	38	Other‡‡: 120

*≥1.5 years from last visit to last Phase I assessment date (1 November 2001); **<1.5 years from last visit to 1 November 2001; †In Phase II, categorization of type of diabetes was not constrained with respect to age at diagnosis but, for comparison purposes, the Phase I classification is presented; ‡In Phase II grandparent country of birth (COB) was ascertained in addition to participant and parents COB leading to an increase in category 5 (mixed). For comparison purposes, the Phase I classification is presented; #There were 317 (22.2%) deaths by 1 November 2011 (end Phase I active follow-up), 603 (42.3%) before Phase II baseline assessments started on 18 February 2008, 727 (51.0%) before Phase II baseline assessments closed; deaths counted in each year if they occurred within 1.5 years of the last assessment; ††Moved overseas during Phase I; ‡‡ Other = no response/return to sender/not on electoral roll (n=115), poor health (n=5)

Table 3. Data collection in FDS Phases I and II.

Questionnaires	1. Demographic details
	2. Diabetes-related information
	3. Current lifestyle measures - in Phase II, this includes specific validated questionnaires relating to diet (**55, 56**) and physical activity (**57, 58**)
	4. Availability of, and access to, care
	5. Knowledge of diabetes - including a validated knowledge test in both Phases (**59**)
	6. General medical information – including, in Phase II, a family history of diseases (**60**) and Berlin sleep (**61**) questionnaires
	7. Current health status – ascertained by General Health Questionnaire (**62**) in Phase I and by multiple validated instruments (**63-66**) in Phase II
	8. Cognitive function, mood and activities of daily and others if indicated clinically – this can include, for Phase II, the Mini-mental State Examination and other validated instruments (**67-69**)
	9. Costs of diabetes – determined from self-reported health service usage and linkage to WADLS and associated databases (**50, 51, 70**)
Clinical examination	1. Anthropometric measures – including, in Phase II, body fat by bio-impedance (**71**).
	2. Cardiovascular status – including autonomic function testing (**72**), auscultation for carotid bruits, Doppler studies for determination of ankle:brachial index, and resting 12-lead electrocardiography.
	3. Respiratory assessment – including spirometry
	4. Neurological assessment – data relevant to the Michigan Neuropathy Screening Instrument clinical score (**73**)
	6. Ophthalmic assessment – including fundus photography in Phase II
	7. Skin autofluorescence – in Phase II only (**74**)
	8. Pulse wave velocity – in a randomly-selected sample of 50% of Phase II patients (**75**)
	9. Overnight home-based sleep studies – in a sub-set of Phase II patients with Berlin scores that are either low risk or high risk for obstructive sleep apnoea
Laboratory tests	1. Serum glucose, glycated haemoglobin, serum urea, creatinine and electrolytes, serum cholesterol, triglycerides, HDL-cholesterol and non-HDL-cholesterol, serum uric acid, liver function tests, urine albumin and creatinine
	2. Glutamic acid decarboxylase antibodies at baseline (Phase I) (**21**)
	3. Full blood count (Phase II).
	4. Extraction and storage of DNA
	5. Aliquots of remaining serum, plasma, urine and whole blood stored at -80ºC for further specialised analyses when required