How did the study come about?

The Geelong Osteoporosis Study (GOS) began as a population-based study designed to investigate the epidemiology of osteoporosis in Australia. Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue, with a consequent increase in susceptibility to fracture. Fragility fractures at the spine, hip, wrist and other sites are a major public health problem in both sexes because these fractures are responsible for considerable morbidity and mortality. Fractures cost the Australian community an estimated $7 billion annually and this is expected to increase in absolute terms because of the ageing population.

The cohort was recruited to address the need for definitive data on the prevalence of osteoporosis, to describe age-related changes in BMD and to characterize the risks for osteoporosis and fracture. Initially the GOS comprised only women; men were recruited later. In addition to the cohort study, the GOS has developed a comprehensive fracture register for the study region and has also conducted case–control studies to investigate risk factors for fracture. Only the cohort study will be described here.

What does the study cover?

The major objectives of this study are to describe the epidemiology of osteoporosis and to generate evidence for defining osteoporosis risk and fracture risk in Australian men and women. We aimed to:

(i) compare BMD and rates of bone loss among various groups of the population;
(ii) compare and combine BMD measurement at different sites to predict fracture risk; and
(iii) generate environmental and genetic evidence to define the risks for osteoporosis and fracture.

Where is the study area?

The study region is described by the Australian Bureau of Statistics (ABS) as the Barwon Statistical Division (BSD), situated in South-Eastern Australia. The BSD comprises the Australian Electoral Commission (AEC) Divisions of Corio, Corangamite (part) and Lalor (part).

Who is in the sample?

Sampling frame

Voting is compulsory in Australia for adults aged ≥18 years, so the electoral roll provides a comprehensive listing of residents registered with the AEC. A listing on the Commonwealth electoral roll as a resident of the BSD fulfilled inclusion criterion for the study. Nationwide census data reported the population of the BSD as 221,687 (108,606 male, 113,072 female) in 1996 (ABS catalogue 2020.0), 241,446 (118,207 male, 123,239 female) in 2001 (ABS 2001.0) and 259,013 (126,889 male, 132,124 female) in 2006 (ABS 2001.0). Persons resident for <6 months and those unable to provide written informed consent were excluded from the study. Population characteristics of the BSD were comparable with national levels for each census; differences did not exceed 1.1% for age, 9.5% for country of birth, 7.5% for school leavers’ age, 2.6% for marital status and 2.1% for weekly income (Table 1).

Participants

An age-stratified sampling method was utilized, involving 12 strata for each sex. Individuals selected at random from the electoral roll were mailed a letter of invitation, with a request to return a response slip or telephone the research centre at Barwon
Health (The Geelong Hospital). Follow-up letters were dispatched to non-responders. At least 100 women and 100 men were recruited in each 5-year age group from 20 to 69 years and 200 of each sex for both the age groups of 70–79 years and ≥80 years. Reasons for non-participation were documented. No indigenous Australians participated. All participants provided written, informed consent at each assessment.

During the years 1993–97, 2390 women were invited to participate, of whom 432 lapsed (Figure 1) and 444 declined to participate, citing personal reasons (53.2%), old age (18%), illness (12.6%), time constraints (10.4%), distance (2.0%), language barrier (1.6%), failure to keep appointments (1.4%) and unknown reasons (0.9%). Thus, there were 1494 female participants, representing a participation of 77%.

Socio-economic status (SES) for participants and non-participants were ascertained using Socio-Economic Index for Areas scores based on census data from the ABS (1996). These data, used to derive an Index of Relative Socio-Economic Disadvantage (IRSD) and categorized into groups according to quintiles of IRSD for the study region, revealed that there were no differences in SES between participants and non-participants ($\chi^2, P = 0.5$).

A new sample of 246 women listed as aged 20–29 years on the 2005 electoral roll was recruited in 2006–08. As this sample has not yet been recalled for follow-up, their details have not been presented.

During the years 2001–06, 3273 men were invited to participate, of whom 167 had died, 311 had left the region, 482 were unable to be contacted and 17 were not able to give informed consent. Of the 2296 remaining, 756 declined to participate due to personal reasons (44%), old age (11%), illness (8%), time constraints (26%), distance (2%), language barrier (2%), failure to keep appointments (2%) and unknown reasons (5%). Thus, there were 1540 male participants representing a participation of 67%. Comparison of participants and non-participants by quintiles of SES

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**Table 1** Maximum differences for population characteristics between the BSD and national levels according to census data collected in 1996, 2001 and 2006

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1996</th>
<th>2001</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (%)</td>
<td>1.0a</td>
<td>0.7a</td>
<td>1.1a</td>
</tr>
<tr>
<td>Country of birth (%)</td>
<td>6.4b</td>
<td>8.0b</td>
<td>9.5b</td>
</tr>
<tr>
<td>School leavers’ age (%)</td>
<td>3.4c</td>
<td>7.5d</td>
<td>7.4d</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td>2.0e</td>
<td>2.2e</td>
<td>2.6e</td>
</tr>
<tr>
<td>Weekly income (%)</td>
<td>2.1f</td>
<td>1.4f</td>
<td>2.0f</td>
</tr>
</tbody>
</table>

*aAge profiles expressed in 5-year age groups from birth to 79 years and ≥80 years. 
*bCountry of birth categorized as Australia vs Canada/Ireland/New Zealand/South Africa/UK/USA vs others.
*cSchool leavers’ age grouped as ≤14 years vs 15 years vs 16 years vs 17 years vs 18 years vs ≥19 years vs still at school vs never attended school.
*dSchool leavers’ age grouped as ≤8 years vs 9 years vs 10 years vs 11 years vs 12 years vs still at school vs did not go to school.
*eMarital status expressed as married vs separated vs divorced vs widowed vs never married.

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**Figure 1** Flow diagram showing number of female participants at each phase of the study and reasons for loss to follow-up
(IRSD, ABS 2001) revealed that there were more than expected non-participants with low SES \( (\chi^2, P < 0.001) \).

**How often have they been followed up and what is attrition like?**

**Females**

The 1494 women recruited at the baseline years 1993–97 were followed by re-assessment phases commencing 1995, 1998, 2000, 2001, 2002 and 2004, referred to as the 2-year, 4-year, 6-year, 7-year, 8-year and 10-year follow-up assessments. Clinical measures were obtained at all phases except the 7-year follow-up. Participation and reasons for loss to follow-up are detailed in Figure 1. Of the eligible women enrolled at baseline, 85% attended the 2-year follow-up. Subsequent phases retained 70% at the 4-year, 86% at the 6-year and 73% at the 7-year follow-up. A subgroup of 325 women was assessed at the 8-year follow-up; 83% of eligible women returned for assessment at the 10-year follow-up.

**Males**

The 1540 men recruited at the baseline years 2001–06 were followed by re-assessment phases commencing 2006 and 2007, referred to as the 5-year and 6-year follow-up assessments; baseline and 5-year follow-up involved clinical assessments. Of the 1540 men enrolled at baseline, 141 had died before the 5-year follow-up, 41 had left the region, 16 were unable to provide informed consent, 139 were not able to be contacted and the remaining 225 declined; the 978 participants represented 81% of eligible men. At the time of writing, the 6-year follow-up was still in progress, so participation details in this phase have not been finalized.

**What has been measured?**

A listing of clinical measures, biochemical and questionnaire data collected at each phase are presented in Table 2.

**Body composition**

Dual-energy X-ray absorptiometry (DXA) provided measures of bone mineral content (BMC) and areal BMD of the lumbar spine (posterior–anterior projection), proximal femur, whole body and forearm (ultradistal and distal 33%). Lateral spine scans were performed at baseline for women; lateral vertebral morphometry was performed at the 10-year follow-up for women and 5-year follow-up for men. Regional and whole body measures of body fat and lean tissue mass were determined from whole body DXA scans. A Lunar DPX-L (Lunar; Madison, WI, USA) was used for the women’s visits and the first 544 men at baseline; when the DPX-L became outdated, male scans were performed using a GE-Prodigy (Prodigy; GE Lunar, Madison, WI, USA). No differences were detected in lumbar spine or femoral neck BMD when cross-calibration was performed on 40 subjects aged 21–82 years. All lateral vertebral morphometry data were obtained with the latter densitometer. Scanning of an anthropomorphic phantom (Hologic) three times per week monitored long-term stability of both machines. Quantitative calcaneal ultrasound was performed using a Lunar Achilles InSight ultrasonometer that provided measures of speed of sound and broadband ultrasound attenuation.

**Anthropometry and other clinical assessments**

Body weight (±0.1 kg) was measured using electronic scales and height (±0.1 cm) using a wall-mounted stadiometer; arm span was measured using a wall-mounted scale and waist (minimal abdominal) and hip (maximum gluteal) circumferences measured with a narrow metal anthropometric tape measure. Blood pressure and pulse rate were obtained using a digital meter and visual acuity assessed using a Snellen chart. Measures of muscle strength were obtained with a manual muscle tester (Nicholas, Model 01160) using a ‘break-test’ technique. The ‘functional reach test’ and timed ‘up-and-go’ test assessed balance and functional mobility. A cumulative sun exposure index compared the skin pigmentation in a UV-exposed site (back of hand and shoulder) with a UV-unexposed site (inner upper arm), as measured with a spectroscope.

**Blood and urine collections**

Blood was collected after an overnight fast for women at baseline and 10-year follow-up, and for men at baseline or 5-year follow-up. Multiple aliquots of serum and plasma were stored at −80°C. DNA was extracted from buffy coats. At baseline, women provided a morning 2-h, second void urine collection after an overnight fast, and women aged 20–29 years also provided a 24-h urine collection.

**Questionnaires**

A series of questionnaires sought information about socio-demographics, quality of life and clinical risk factors including exposure to disease, use of medications and supplements, diet, mobility, physical activity, sun exposure, sleep, falls and fractures, alcohol and tobacco use, reproductive history and sexual functioning, family history of fractures and diseases,
## Table 2  Measurements for each follow-up phase, indicated by year of commencement for women and men enrolled in the GOS cohorts

<table>
<thead>
<tr>
<th>Phase</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline 1993</td>
<td>Fasting blood samples taken, DNA extracted, fasting glucose, albumin, calcium, phosphate assayed, serum/plasma aliquots stored at $-80^\circ$C. Subsequent analyses for 25-hydroxyvitamin D, parathyroid hormone, $\beta$-isomerized C-terminal telopeptide, bone-specific alkaline phosphatase and procollagen type 1 N-terminal peptide, leptin, cholesterol, vitamin B12 and high sensitivity C-reactive protein. 2-h timed morning urine collection; urinary calcium, phosphate, creatinine assayed, aliquots stored at $-20^\circ$C. 24-h urine collection (age &lt;30 years). Anthropometric measures: weight, height, waist and hip circumferences, arm span. Blood pressure. Bone densitometry (DXA)—multi-site. Socio-economic status. Questionnaire: self-reported exposure to drugs (coded according to the structured drug codes developed by the Society of Hospital Pharmacists, Victorian Branch, 1986) and diseases, falls and fracture history, family fracture history, smoking (current and past patterns of tobacco smoking included manufactured and ‘hand-rolled’ cigarettes, cigars and pipes), alcohol consumption (frequency, quantity and type), mobility, use of walking aid, education, marital status, occupation [using Australian Standard Classification of Occupation (ABS, 1986), based on skill level and specialization], employment status (self and partner), birth place, ethnicity, reproductive history, sun exposure (current and past practices, use of sunscreens, skin type and propensity to burn), bowel syndrome. Diet.</td>
</tr>
<tr>
<td>7-year follow-up 2001</td>
<td>Questionnaire only: falls and fractures.</td>
</tr>
</tbody>
</table>

(continued)
Table 2 Continued

<table>
<thead>
<tr>
<th>Phase</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-year follow-up 2004</td>
<td>Fasting blood samples taken, DNA extracted, serum/plasma aliquots stored at −80°C. Anthropometric measures: weight, height, waist and hip circumferences, arm span.</td>
</tr>
<tr>
<td></td>
<td>Socio-economic status. Questionnaire: self-reported exposure to drugs and diseases, falls and fractures, family medical history, smoking, alcohol consumption, mobility, occupation, sun exposure.</td>
</tr>
</tbody>
</table>

Men

Baseline 2001

Fasting blood samples taken, DNA extracted, serum/plasma aliquots stored at −80°C; subsequent analyses for β-isomerized C-terminal telopeptide, procollagen type 1 N-terminal peptide, glucose and vitamin B12.


5-year follow-up 2006


6-year follow-up 2007

Questionnaire only: falls and fractures.
mental health, pain, quality of life and well-being (Table 2):

(i) residential address for each individual was linked to the corresponding ABS Census Collection District, and ABS software utilized to derive the area-based Socio-economic Index for Areas scores, providing a set of summary Indexes of relative SES;

(ii) mobility was reported in categories ranging from ‘very active’ to ‘unable to walk’ (Table 3);

(iii) descriptions of physical activity intensity categories were based on Metabolic Equivalent of Task values\(^3\) (Table 3). Habitual physical activity scores were also derived for three distinct dimensions: physical activity at work, sport during leisure-time and other physical activity during leisure-time;\(^1\) a questionnaire for the elderly was used for ages \(\geq 60\) years;\(^7\)

(iv) self-reported fractures were verified from radiological reports.\(^3\) Falls were recalled over the preceding year. A fear of falling\(^1\) and falls risk\(^4\) were also assessed;

(v) details of age of menarche, menopause, pregnancies, births, amenorrhea, breastfeeding, exposure to gonadal hormones, surgery and radiotherapy were documented for women (Table 3). Men completed the androgen deficiency in aging males questionnaire;\(^\) and

(vi) in addition to self-report questionnaires assessing mental health, mood and anxiety disorders were diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Non-patient edition (SCID-I/NP).\(^2\)

What has been found?

Data generated from the GOS cohort has produced 90 publications in peer-reviewed literature and 150 presentations at national/international meetings.

BMD

We have reported on the:

(i) prevalence of osteoporosis and osteopenia\(^6\),\(^3\) using World Health Organization guidelines based on BMD deficits;

Table 3 Details of categories presented as alternatives in questionnaires

<table>
<thead>
<tr>
<th>Topic</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>Very active: moves, walks and works energetically and participates in vigorous activity; Active: walks at brisk pace, does normal housework or other work and engages in light exercise; Sedentary: walks reasonable distances, does light housework, shopping or equivalent and normal activities of day-to-day living but no appreciable exercise; Limited: little walking outside home, but prepares meals and does very light housework or equivalent; Inactive: sits in chair or lies in bed most of the time, walks independently from bed to chair to toilet but requires assistance for greater movement; Chair or bed-ridden: cannot walk from bed to chair to toilet without considerable assistance; Bedfast: unable to walk (even with a walking aid)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Very hard: regular participation in strenuous pursuits involving a lot of movement or running (e.g. carrying heavy loads of bricks or timber, digging ditches, chopping wood, jogging, footfall, uphill cycling); Hard: regular participation in vigorous pursuits (e.g. construction work, tennis, downhill skiing, pushing a non-powered mower and swimming laps); Moderate: regular pursuits involving moderate physical activity (e.g. brisk walking, leisurely cycling, sweeping, vacuuming, raking lawn, pushing child in pusher, carpentry); Light: most activities involving sitting, standing or slow walking (e.g. typing, ironing and bowling)</td>
</tr>
<tr>
<td>Surgery/radiotherapy to female organs</td>
<td>No surgery; Hysterectomy (including removal of ovaries); Hysterectomy (leaving one ovary in place); Removal of one ovary; Removal of both ovaries; Radiotherapy to ovaries</td>
</tr>
</tbody>
</table>
Fracture risk calculator

The development of a clinically useful fracture risk (FRISK) equation was based on two-site areal BMD, falls, previous fracture and weight. The calculator is accessible on-line (http://www.oscal.com/Reduce_Frisk_Calc.aspx). Fracture risk expressed as a FRISK score can be converted to absolute risk for fracture. Estimation of BMD cut-off values that confer equivalent fracture risk in elderly women to those with osteoporosis and fracture contributed to Health Insurance Commission subsidy for BMD and Pharmaceutical Benefits Advisory Committee subsidy for primary prevention therapy in Australia.

Risk factors for bone fragility

GOS data were the first to show that increased circulating concentrations of high-sensitivity C-reactive protein are associated with increased fracture risk, suggesting that the inflammatory marker could be used as a prognostic marker. An association between circulating leptin levels and BMD in humans suggested that leptin mediates the link between body fat mass and BMD. Exposure to statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) for the treatment of hypercholesterolemia was associated with reduced fracture risk, an effect not entirely explained by increased BMD. An association between β-blocker use and reduced fracture risk supported the hypothesis that bone metabolism is modulated by the adrenergic nervous system; a cross-sectional association between β-blocker use and a reduced level of bone resorption marker in early post-menopausal women further supported this notion. Depression is associated with low BMD and the finding that exposure to selective serotonin re-uptake inhibitors, used in the treatment for depression, is associated with BMD deficits was consistent with a role for the serotonergic system in regulating bone metabolism. We have reported that paracetamol (acetaminophen) use is associated with increased fracture risk, exposure to oral contraceptives is associated with greater lumbar BMD and hormone therapy is protective against non-vertebral fracture. We demonstrated that post-menopausal women with and without hip fractures had different hip structures; furthermore, femoral neck dimensions seemed unlikely to be associated with age of menarche. Women from both ends of the socio-economic spectrum were shown to have low BMD; this was also observed for young men, whereas the pattern was reversed for older men. An inverse relationship was observed between SES and hip fracture.

Lifestyle and skeletal health

We described seasonal periodicity in circulating concentrations of 25-hydroxyvitamin D (25OHD); reduced serum 25OHD coincided with increased serum parathyroid hormone and increased serum bone resorption markers in winter. An ecological study suggested that this periodicity was associated with an increased proportion of falls resulting in fracture and an increased risk of wrist and hip fractures in late winter. These findings informed the design of a randomized controlled trial of high dose annual vitamin D for the prevention of falls and fracture. We also reported greater BMD among women with higher serum 25OHD and among men with the metabolic syndrome.

Nutrition

Dietary intakes of calcium, vitamin D, caffeine and selenium have been described at a population level, together with behavioural and physical characteristics associated with vitamin D status and an association between antioxidant vitamin supplements and markers of bone turnover. We have commented on the patterns of alcohol use, the paradoxical nutritional deficiency in overweight and obesity, temporal increases in adiposity and the association of SES with obesity and metabolic disorders.

Other outcomes

We estimated the increase in the number of women in Australia diagnosed with diabetes following the decision of the Australian Diabetes Association to lower the fasting blood glucose level for the diagnosis of diabetes from 7.8 to 7.0 mmol/L. We tested the utility of the Australian Diabetes Risk Assessment Tool, a score developed by AusDiab, for predicting incident diabetes, and an increased fracture risk associated with rosiglitazone was demonstrated as being largely a consequence of increased body weight.

Collaborations

In collaboration with the Barwon Psychiatric Research Unit, we reported the prevalence of the common mental disorders in Australia and identified tobacco smoking, physical inactivity, poor diet and
systemic inflammation as associated with increased risk for mood disorders. In collaboration with the Genomics Research Centre, Griffith University, DNA polymorphism within runt-related gene 2 [RUNX2/ core binding factor A1 (CBFA1)] was related to BMD. DNA from the GOS was included in the Australian Genome-wide Association Study, which has identified other novel genes controlling BMD and fracture. Collaborative work with Monash University revealed that obesity and weight gain in healthy young women increase the risk for osteoarthritis of the knee.

What are the main strengths and weaknesses of the study?
The major strength of the study is that participants were selected at random from the general population. The BSD provides an excellent base for epidemiological research, as the region’s population is large enough and suitably diverse to resemble the broader White Australian community. The processes of recruitment, the attainment of clinical measures and development of a biospecimens’ repository, with ongoing documentation of numerous health outcomes, lifestyle and socio-demographic factors for large numbers of study participants has been both labour-intensive and expensive, yet we have recruited well and avoided excessive loss to follow-up. Although low participation in cohort studies has minimal impact on estimates of relative risk, our baseline participation of 77% for women and 67% for men provided robust platforms for estimating the disease prevalence and developing normative datasets. High retention rates (women: 86% at 6-year follow-up and 83% at 10-year follow-up; men: 81% at 5-year follow-up) are important for the validity of the study.

Access to Commonwealth electoral rolls provided a comprehensive sampling framework from which our random samples could be generated. However, as a consequence of temporal changes, Australia’s immigration trends and slower changes in the BSD, the cohort lacks the ethnic diversity of today’s population. According to the 1996 census, there was a 6.4% excess of Australian-born individuals in the BSD compared with national profiles and this rose to 9.5% by 2006, the differential driven by a smaller proportion of BSD residents who have migrated from Asia or the Middle East countries. Furthermore, the majority of our cohort are White. These factors combined may limit the generalizability of the study findings.

Clinical assessments were performed using standardized techniques, incident fractures ascertained from radiology reports and major medical outcomes confirmed from medical histories. However, we relied on self-reported data to document minor medical events and lifestyle choices. The GOS has archived biochemical, genetic, clinical, lifestyle and socio-demographic data that afford the opportunity to identify risk factors for the development and progression of future disease and health disorders in addition to our major focus, which is osteoporosis.

Can I get hold of the data? Where can I find out more?
Information about the GOS and details about publications and conference presentations can be accessed through the Barwon Health website at: http://www.barwonhealth.org.au/research/keyresearchprojects/default.aspx. Data from the cohort are archived by the Barwon Epidemiology and Biostatistics Unit. Requests for access to the data and establishment of collaborative projects are dealt with by an oversight committee comprising representatives of the Principal Investigator group and the Barwon Health Human Research Ethics Committee.

Funding
The work was supported in the early 1990s with funding from the Victorian Health Promotion Foundation (ID 91-0095); subsequent core funding was secured from the National Health and Medical Research Council (ID 251638, ID 299831, ID 628582); the Geelong Region Medical Research Foundation; Barwon Health, Perpetual Trustees; the Dairy Research and Development Corporation; the University of Melbourne; the Ronald Geoffrey Arnott Foundation; ANZ Charitable Trust; the American Society for Bone and Mineral Research and Amgen (Europe) GmbH. The study was approved by the Barwon Health, Human Research Ethics Committee (ID 92/01 and ID 00/56).

Acknowledgements
We thank current and past staff for their efforts in recruiting the cohorts and obtaining and processing the data. Thanks are also extended to study participants.

Conflict of interest: None declared.
KEY MESSAGES

- The primary focus of the GOS is to describe the burden of osteoporosis in the general population and to identify risk factors for fracture.
- The large prospective cohort study was initiated in 1993; since then 1494 women and 1540 men, randomly selected from the electoral rolls, return to the study centre at Barwon Health every few years to have their bone mineral density measured and their health monitored.

References


