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Association between knee symptoms, change in knee symptoms over 6–9 years, and SF-6D health state utility among middle-aged Australians

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Abstract

Objectives Health state utilities (HSUs) are an input metric for estimating quality-adjusted life-years (QALY) in cost–utility analyses. Currently, there is a paucity of data on association of knee symptoms with HSUs for middle-aged populations. We aimed to describe the association of knee symptoms and change in knee symptoms with SF-6D HSUs and described the distribution of HSUs against knee symptoms' severity.

Methods Participants (36–49-years) were selected from the third follow-up (completed 2019) of Australian Childhood Determinants of Adult Health study. SF-6D HSUs were generated from the participant-reported SF-12. Association between participant-reported WOMAC knee symptoms' severity, change in knee symptoms over 6–9 years, and HSUs were evaluated using linear regression models.

Results For the cross-sectional analysis, 1,567 participants were included; mean age 43.5 years, female 54%, BMI ± SD 27.18 ± 5.31 kg/m^2. Mean ± SD HSUs for normal, moderate, and severe WOMAC scores were 0.820 ± 0.120, 0.800 ± 0.120, and 0.740 ± 0.130, respectively. A significant association was observed between worsening knee symptoms and HSUs in univariable and multivariable analyses after adjustment (age and sex). HSU decrement for normal-to-severe total-WOMAC and WOMAC-pain was − 0.080 (95% CI − 0.100 to − 0.060, $p < 0.01$) and − 0.067 (− 0.085 to − 0.048, $p < 0.01$), exceeding the mean minimal clinically important difference (0.04). Increase in knee pain over 6–9 years was associated with a significant reduction in HSU.

Conclusion In a middle-aged population-based sample, there was an independent negative association between worse knee symptoms and SF-6D HSUs. Our findings may be used by decision-makers to define more realistic and conservative baseline and ongoing HSU values when assessing QALY changes associated with osteoarthritis interventions.

Keywords WOMAC · Health state utility · Osteoarthritis · SF-6D · QALY · Population norm

Introduction

Joint pain is the most prevalent musculoskeletal condition causing physical and psychosocial disability, and affecting millions of people and societies globally from both a humanistic and economic perspective [1, 2]. Knee pain is the most pervasive type of joint pain among adults older than 18 years and is reported by one in every two adults aged 50 years or older [3, 4]. A common cause of knee pain in the elderly population is knee osteoarthritis (OA), a chronic, progressive musculoskeletal disorder [5]. Importantly, the health-related quality-of-life (HRQoL) burden for knee pain in a younger (namely middle-aged) population worldwide is not well investigated and a younger

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cohort's knee pain may translate to knee OA for many people who suffer knee pain, particularly as they reach older age and older age cohorts.

The global prevalence of knee OA was estimated to be more than 350 million people in 2019, and more than 2 million people had knee OA in Australia in the year 2019 [5, 6]. The economic burden of joint pain is also substantial [7]. Among patients with knee OA, knee pain has been recognized as a significant reason for knee replacement [8]. OA imparts a substantial economic burden to health systems globally; in Australia alone, it accounted for $3.5 billion of direct healthcare costs and $23 billion for total costs, including the indirect and intangible costs (for example, lost work productivity and loss of well-being) [5, 9, 10].

Knee OA is characterized by knee pain, stiffness, and physical dysfunction leading to limitations for activities of daily living and consequent diminution of HRQoL [11]. Various studies using both disease-specific patient-reported outcome (PRO) instruments such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [12, 13], Knee injury and Osteoarthritis Outcome Score (KOOS) [8, 14], and generic PRO instruments such as the EuroQol-5 suite of instruments (EQ-5D-3L and 5L) [14], Short-Form-6 Dimension (SF-6D) [15], 12-item Short-Form Survey (SF-12) [8, 16], and 36-item Short-Form Health Survey (SF-36) [13] have reported a severe impact of the presence of knee pain on HRQoL in patients with knee OA. Disease-specific HRQoL instruments (such as the WOMAC and KOOS) provide valuable disease-specific information from the patient's perspective and are highly sensitive to detect the minimal clinically important difference (MCID) in knee pain in OA [17, 18]. However, these instruments are profile-based measures and, therefore, not recommended to generate preference-based scores called health state utility (HSU) values needed for health economic analyses [19]. Generic PRO instruments, also called preference-based HRQoL instruments or multi-attribute utility instruments (such as the SF-6D [20], EQ-5D-5L and 3L [21], AQoL-8D [22], and HUI [23]), generate these patient-reported quantitative preference-based measures of HRQoL called HSU [24–26]. More specifically, HSUs are a health economic measure on a scale of 0.0–1.0 that provide the strength of preference an individual places on a particular health state relative to the states of perfect health (namely HSU = 1.0) and death (HSU anchored at a value of 0 and some instruments assign HSUs at less than 0 for health states considered worse than death) [25, 27, 28]. Importantly, multi-attribute utility instruments that assess HSUs are routinely used to evaluate the quality of life for patients with knee OA and are now gaining importance as the preferred outcome measure in patients reporting knee pain [8].

Quality-adjusted life-years (QALYs) are an outcome metric routinely used in health economic evaluations, particularly cost–utility analysis (CUA) [29–31]. QALYs incorporate both the quantity and quality of life, and therefore allow a broader comparison across varying patient populations, treatment strategies, and clinical settings [29, 30]. The duration spent in a particular health state (survival) provides the quantity component, and the HSU assigned to the specific health state provides the quality (HRQoL) component for QALY calculation, which is simply a product of survival and HSU (i.e., quantity and quality) [29, 30].

Markov modelling is often used as a tool to estimate the economic and humanistic burden for chronic conditions such as knee pain and knee OA [27, 28]. Importantly, for accurate estimation of the humanistic burden, it is essential to assign *evidence-based HSUs* to patients entering the model, rather than simply assuming these patients to be at an HSU of 1.0 (that is perfect health) [32]. A typical Markov model for CUA starts with a cohort of people at risk of a disease (knee pain, knee OA) and simulates the transition of the study population between discrete health states [33, 34]. The transition is governed by transition probabilities and has an associated HSU for each health state occurring within a defined period called the Markov cycle [35]. Hence, evidence on HSUs for this cohort and how knee-symptom severity affects HSUs may enable appropriate assumptions for CEA models and health economic decision making. Utilities have also been shown to be independent predictors of patient outcomes, including all-cause mortality and development of complications [36]. Additionally, clinicians have found that measuring health utilities is of benefit to patients regarding clinical assessment, relationships, communication, and management [37]. Thus, understanding the characteristics of the disease, such as knee pain and its impact on HSUs, is of utmost importance to promote value-based care and informed resource allocation.

Although previous studies have reported HSUs for knee OA patients and highlighted the detrimental effect of knee pain on quality of life in older adults and patients with knee OA [38], there is a paucity of literature regarding the HSUs for a general population entering an OA health economic model and little is known about the association of knee pain, stiffness, and dysfunction with HSU in younger adults [39–43].

Against the backdrop of a paucity of literature that assesses HSUs for a relatively younger population with knee pain, to our knowledge, this will be the first study to explore the association of knee symptoms and HSUs in a sample largely representative of the Australian middle-aged population. Therefore, we aimed to describe the distribution of HSUs against knee-symptom severity classifications and the impact of change in knee symptoms over 6–9 years on HRQoL using the SF-6D's HSUs.

Methods

Study participants and data collection

The study sample was selected from the Childhood Determinants of Adult Health (CDAH) study, a three-phase follow-up of participants in the Australian Schools Health and Fitness Survey (ASHFS). The study designs of CDAH and ASHFS have been described elsewhere; here, we provide a summary [44, 45]. ASHFS was a nationwide survey comprising a sample of 8498 school children aged 7–15 years (mean age 11) for whom a wide range of health-related measures was collected in the year 1985. Figure 1 shows the flow of participants from the ASHFS into the CDAH cohorts. The first follow-up of the ASHFS sample for the CDAH study comprised 3521 participants and was conducted in 2004–2006 (referred to as the CDAH-1) [46–48]. The second follow-up (referred to as CDAH-2) consisted of 2815 participants and was conducted during 2009–2011 [47, 48]. During the same time, an ancillary study (referred to as CDAH-knee study) consisting of 449 CDAH participants was introduced to assess the impact of early life risk factors on knee structure and symptoms. The third follow-up (referred to as CDAH-3) comprised a sample of 1568 participants and was conducted in 2014–2019.

Our cross-sectional study sample (Fig. 1, bottom curly bracket) was derived from CDAH-3 ($n = 1567$: aged 36–49 years, female 54%). We included data for participants who completed the SF-12 and knee WOMAC questionnaires and provided other clinical characteristics at the CDAH-3 follow-up study. For our longitudinal analysis (Fig. 1, right curly bracket), participants were selected who completed the CDAH-knee study [49] ($n = 313$; age mean ± standard deviation (SD) = 34.94 ± 2.72 years; female = 48%) and were matched to CDAH-3 data after 6–9 years ($n = 313$; age mea n ± SD = 42.84 ± 3.38 years).

All the participants of the CDAH-knee and CDAH-3 studies provided written informed consent, and the studies were approved by the Southern Tasmania Health and Medical Human Research Ethics Committee, Monash University Human Research Ethics Committee, and the Northern Sydney and Central Coast Area Human Research Ethics Committee.

Anthropometric measurements

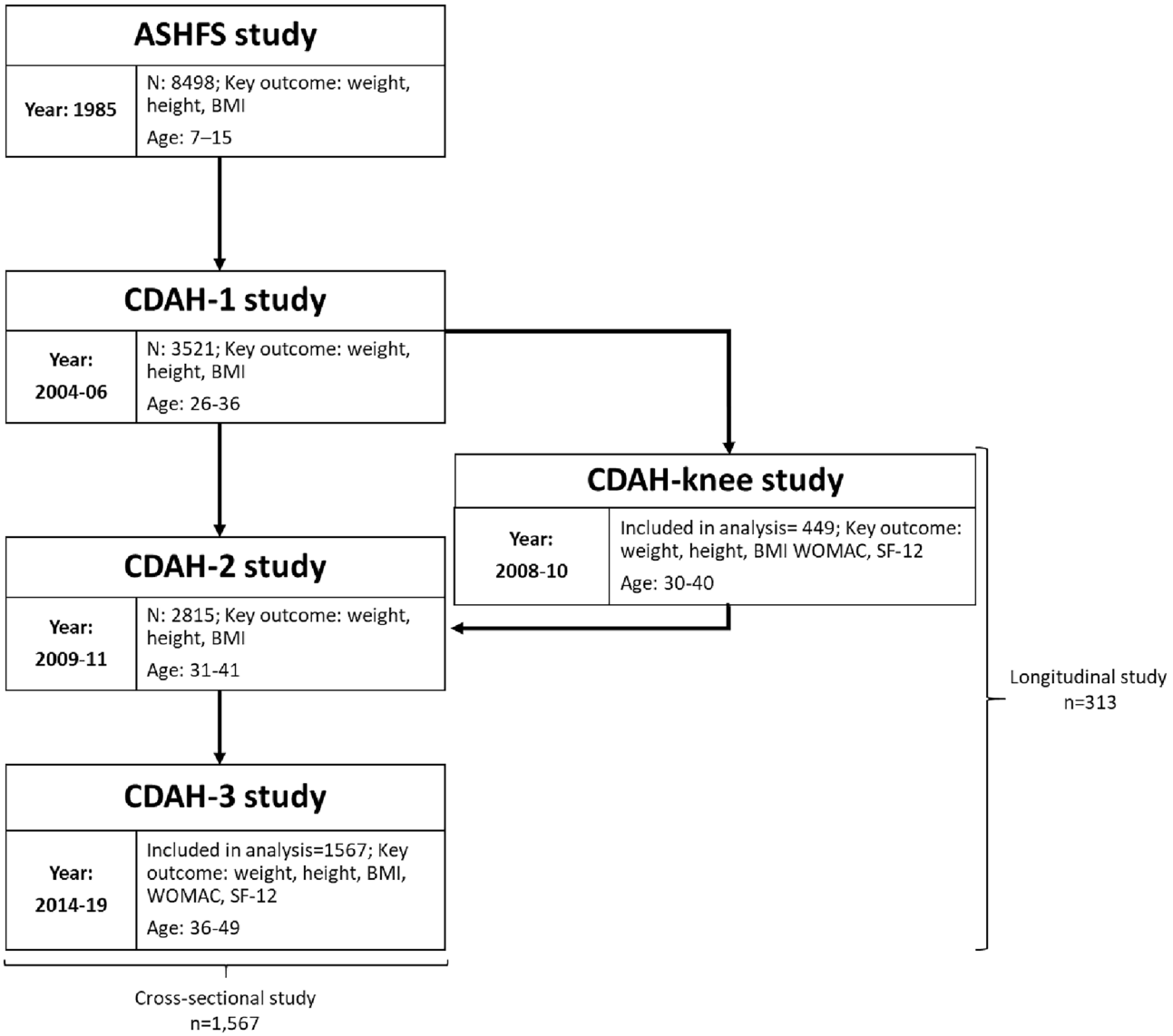
At the CDAH study, weight was measured to the nearest 0.1 kg and with shoes, socks, and bulky clothing removed. Height was measured to the nearest 0.1 cm with shoes and socks removed using a Leicester stadiometer (Invicta, Leicester, UK) [49]. Body mass index (BMI) was calculated from height and weight as kilograms of weight per square meter of height (kg/m^2) [50]. BMI was categorized as underweight ($< 18.5\ kg/m^2$), healthy weight (≥ 18.5 and $\leq 24.9\ kg/m^2$), overweight (≥ 25.0 and $\leq 29.9\ kg/m^2$), and obese ($\geq 30\ kg/m^2$) [51]. Sociodemographic and clinical data on other participant characteristics such as education and comorbidity were self-reported in childhood and follow-up.

Knee symptom measurements

Data on knee pain and symptoms were collected through questionnaires in CDAH 3 study and computer-assisted telephone interviews (CATI) in the CDAH-Knee study. The WOMAC instrument was used to assess the knee pain, stiffness, and physical dysfunction captured on a scale of "0–9", where "0" indicated no pain, stiffness, or dysfunction, and "9" indicated the maximum observed pain, stiffness, and dysfunction [18]. Although the WOMAC is a preferred disease-specific PRO instrument for patients with OA, it is also validated for responsiveness to knee pain and symptoms in young study populations without OA [17, 52]. The WOMAC instrument captured and assessed knee pain under five subscales with the highest possible score of 45, and stiffness and dysfunction were captured under 2 and 17 subscales with the highest possible scores of 18 and 153, respectively. The overall WOMAC score was calculated as a sum of scores for each subscale with the highest possible score of 216. Score ≥ 1 for respective domains of WOMAC was indicative of pain, stiffness, and dysfunction. The knee pain was categorized as: no pain (WOMAC-pain score = 0), moderate pain (score ≤ 5), and severe pain (score > 5) [53, 54]. Stiffness was categorized as, no stiffness (WOMAC-stiffness score = 0), moderate stiffness (score ≤ 2), and severe stiffness (score > 2). Physical dysfunction was categorized as: no function limitation (WOMAC-function score = 0), moderate function limitation (score ≤ 17), and severe function limitation (score > 17) [55].

SF-6D HSUs for people with knee pain

We used the SF-12 (version 2) questionnaire to capture the patient-based assessments of HRQoL at the CDAH-knee and CDAH-3 follow-ups. The SF-6D is a globally prevalent multi-attribute utility instrument derived from the patient-reported responses to the SF-36 or SF-12 questionnaire [24]. More specifically, the SF-6D assesses HSUs for 18,000 health states, and has been well validated for complex and chronic disease states and has an equal preponderance to both physical and psychosocial health needs [56]. HSUs for our study population were derived from the patient-reported response to the SF-12 and then calculated through the SF-6D's algorithm based on the UK value set in the absence of an Australian value set for the SF-12 [24, 57]. The HSU



ASHFS, Australian Schools Health and Fitness Survey; BMI, body mass index; CDAH, childhood determinants of adult health; N, number of patients at the respective time point; SF-12, 12-Item Short Form Survey; WOMAC, Western Ontario MacMaster osteoarthritis score.

Fig. 1 Participant flowchart

value generated by the SF-6D's algorithm ranges from 1.00 (best HRQoL state or perfect health) to 0.30 (worst HRQoL state measured by the SF-6D) [24].

We adopted the previously reported minimal important difference (MID) (or minimal clinically important difference (MCID)) for the SF-6D's HSUs at a mean of 0.04 to assess the significance of the HSUs variation across the knee-symptom severity groups [58, 59]. In the absence of knee pain-specific MID or MCIDs for the SF-12 variant of the SF-6D, we have adopted a slightly more conservative estimate of composite measures that have used the SF-36 variant of the SF-6D. To illustrate, the reported measure for knee OA by Brazier et al. (2005) is 0.035 utility points, and for rheumatoid arthritis is 0.037 utility points [59, 60]. Additionally, a paper that investigated both the SF-12 and SF-36 variants of the SF-6D for a study population with spinal cord injuries suggested that the SF-6D of either derivation was suitable for detecting the clinical change for that study [61]. We also adopted the previously reported UK and Australian population norms, including population norms for the UK middle-aged cohort of 45–49 (0.79 utility points), and Australian middle-aged cohort deciles of 31–40 years (0.79 utility points) and 41–50 years (0.77 utility points), and these mean HSUs are similar for both countries [62, 63].

Statistical methods

Summary data describing the sociodemographic characteristics of the participants at CDAH-knee and CDAH-3 follow-ups are presented as means with standard deviations (SDs) for continuous variables, and as percentages with frequency counts for categorical variables. Comparison of the mean values of age, weight, and BMI of two groups of participants (those for whom an SF-6D HSU could be generated or not—i.e., with and without SF-6D HSU) were performed using two-sample *t*-tests. Univariable and multivariable linear regression was performed to estimate the association between WOMAC knee symptom (knee pain, stiffness, and dysfunction) scores and SF-6D HSU before and after adjustment for confounders. The outcome variable (SF-6D HSU) was transformed (for example by taking logarithms) prior to analysis to reduce positive skewness. Importantly, the estimates reported have been back-transformed to the original scale of the HSU. In the development of the multivariable regression models, confounding and statistical interaction were assessed with covariates for age, sex, BMI, education, and co-morbidities including diabetes and hypertension. Results are reported without and with adjustment for age and sex. The cross-sectional analyses are reported with additional adjustments for BMI and education. Tests of interaction did not reach statistical significance, but results for subgroup analyses for sex (male and female), age (36–40 years, 41–45 years, and > 45 years), and BMI (underweight, healthy weight, overweight, and obese) are reported. In longitudinal analyses, covariates for education, diabetes, and hypertension were significant predictors of the outcome, but adjustment with these factors did not markedly alter the estimated coefficients of the covariates for the WOMAC measures. The longitudinal analyses included regression of HSU on change in WOMAC scores, and of change in HSU on WOMAC scores and on change in WOMAC scores. The changes were calculated by subtracting the values of HSU and WOMAC at CDAH-knee from the respective values at CDAH-3. To check the robustness of the findings to the statistical methods used, the linear regression estimates were compared with those from truncated regression models that acknowledged the upper and lower limits of the measured range of the SF-6D HSUs. Providing confidence in the robustness of the results, the estimates were barely changed. Only participants who had complete data on all covariates and the outcome of interest were included in the models; no data were imputed. A p-value of < 0.05 was considered statistically significant. All analyses were performed using STATA software, version 16.0 (Stata Corp.).

Results

Participant characteristics

Our cross-sectional analysis sample included 1567 participants from the CDAH-3 study. The anthropometric characteristics of participants in the cross-sectional sample are shown in Table 1. Briefly, the mean ± SD age of the population was 43.5 ± 2.9 years, with females constituting 54% of the sample, and overall mean ± SD BMI was 27.18 ± 5.31 kg/m^2. The mean (SD) total-WOMAC score was 10.20 ± 21.47, and the mean (SD) HSU value was 0.79 ± 0.12 ranging from 0.39 to 1.

Our longitudinal analysis sample included 313 participants followed from CDAH-knee to CDAH-3 (Online Appendix 1, Table 1). The mean ± SD age was 34.94 ± 2.72 and 42.84 ± 3.38, at CDAH-knee and CDAH-3, respectively. The mean ± SD total-WOMAC scores were 6.26 ± 12.64 and 6.62 ± 13.99, and the mean ± SD HSU values were 0.790 ± 0.120 and 0.800 ± 120, at CDAH-knee and CDAH-3, respectively. The participant characteristics were comparable in terms of age, weight, and BMI for males and females for whom an SF-6D HSU could be generated or not generated from the SF-12 patient-reported responses ($p < 0.05$) (Online Appendix 1, Table 6).

Table 1 CDAH-3 population descriptive characteristics

Participants' characteristics ($n = 1567$)	% (n)	Mean ± SD
Age, years	100 (1567)	43.50 (2.92)
Age group, % (*n*)		
36–40	263 (16.78%)	
41–45	677 (43.20%)	
> 45	627 (40.01%)	
Sex		
Male, % (*n*)	46.08 (722)	
Female, % (*n*)	53.92 (845)	
Weight	99.36 (1557)	80.86 ± 18.02
BMI, kg/m^2	99.36 (1557)	27.18 ± 5.31
Total WOMAC score	85.58 (1341)	10.21 ± 21.47
WOMAC-pain	85.64 (1342)	2.65 ± 5.30
WOMAC-pain yes, % (n)	43.29 (581)	
WOMAC-stiffness	85.64 (1342)	1.48 ± 2.70
WOMAC-function	85.96 (1347)	6.07 ± 14.56
HSU	97 (1520)	0.79 ± 0.12

BMI body mass index, *HSU* health state utility, *n* number of patients at the respective time point, *WOMAC* Western Ontario MacMaster osteoarthritis score

*All data are presented as mean SD unless otherwise stated

HSUs and WOMAC categories

Table 2 presents the WOMAC score for various categories and the corresponding HSUs for the cross-sectional analysis. The mean ± SD HSU for normal, moderate, and severe total-WOMAC scores were 0.820 ± 0.120, 0.800 ± 0.120, and 0.740 ± 0.130, respectively. Demonstrating a consistent trend, participants with normal WOMAC score (WOMAC = 0) had a consistently higher HSU value than participants in moderate and severe WOMAC score groups across the categories of total-WOMAC, WOMAC-pain, WOMAC-stiffness, and WOMAC-function. Additionally, the difference between participants classified in the normal or mild disease severity classification compared to the severe disease severity classification exceeded the MCID of 0.04 utility points for the SF-6D [58, 59]. Importantly, this demonstrates the discriminatory power of the SF-6D to appropriately differentiate according to the disease severity classifications with reduced HSUs for increasing disease severity confirming the discriminatory validity of the SF-6D HSU values for this population. Although a smaller sample size, similar trends were observed for the longitudinal sample (Table 2).

Association of knee symptoms and HSUs

Table 3 shows the associations between various WOMAC groups and SF-6D HSU values for the CDAH-3 cross-sectional analysis. Importantly, a significant association was observed between worse knee symptoms and HSUs in univariable and multivariable analyses after adjustment for age and sex. The HSU decrement for normal-to-severe total-WOMAC and WOMAC-pain groups was − 0.080 (95% CI − 0.100 to − 0.060, $p < 0.01$) and − 0.067 (− 0.085 to − 0.048, $p < 0.01$), exceeding the MCID (0.04 utility points). Based on the linear regression coefficient, the SF-6D HSU value exceeded the MCID of 0.04 at the WOMAC score of 33, 9, 5, and 22 for total-WOMAC, WOMAC-pain, WOMAC-stiffness, and WOMAC-function. Consistently across groups (i.e., total-WOMAC, WOMAC-pain, WOMAC-stiffness, and WOMAC-function), a worse WOMAC score was associated with a statistically significantly stronger detrimental impact on HSUs demonstrated by lower beta coefficient value. Table 4 shows the longitudinal association between WOMAC score at the CDAH-knee and CDAH-3 follow-ups and HSU value at CDAH -3. Knee pain at CDAH-knee was significantly associated with a reduction in HSU 6–9 years later at the CDAH-3 follow-up [adjusted regression coefficient = − 0.004 (− 0.008 to − 0.001; $p = 0.038$)]. Similarly, a consistent trend was observed across the knee symptoms (WOMAC total, pain, stiffness, and function) at CDAH-knee and HSU at CDAH-3 follow-up. Participants with worsening WOMAC scores over 6–9 years had a lower HSU, compared to those with stable/decreased WOMAC over the same period (Fig. 2). Participants with

Table 2 WOMAC categories and corresponding mean health state utility at CDAH-3 and CDAH-knee follow-ups

WOMAC categories	CDAH-3			CDAH-knee		
	n	WOMAC *Mean ± SD*	HSU *Mean ± SD*	*n*	WOMAC *Mean ± SD*	HSU *Mean ± SD*
Total WOMAC overall	1341	10.21 ± 21.47	0.790 ± 0.120	312	6.27 ± 12.65	0.800 ± 0.120
WOMAC (score = 0)	588	–	0.820 ± 0.120	144	–	0.810 ± 0.110
Moderate WOMAC (score ≤ 24)	583	7.40 ± 6.02	0.800 ± 0.120	146	6.90 ± 5.53	0.790 ± 0.120
Severe WOMAC (score > 24)	170	55.16 ± 33.28	0.740 ± 0.130	22	43.18 ± 21.48	0.770 ± 0.120
WOMAC-pain overall	1342	2.65 ± 5.30	0.790 ± 0.120	312	1.57 ± 3.29	0.800 ± 0.120
No pain (score = 0)	761	–	0.820 ± 0.110	204	–	0.800 ± 0.110
Moderate pain (score ≤ 5)	374	2.51 ± 1.41	0.790 ± 0.120	70	2.46 ± 1.31	0.810 ± 0.110
Severe pain (score > 5)	207	12.65 ± 7.27	0.750 ± 0.130	33	9.39 ± 4.56	0.760 ± 0.130
WOMAC-stiffness overall	1342	1.48 ± 2.70	0.790 ± 0.120	312	1.05 ± 2.15	0.800 ± 0.120
No stiffness (score = 0)	839	–	0.810 ± 0.120	214	–	0.820 ± 0.110
Moderate (score ≤ 2)	228	1.57 ± 0.50	0.800 ± 0.120	51	1.57 ± 0.50	0.770 ± 0.130
Severe (score > 2)	275	5.92 ± 3.02	0.770 ± 0.120	47	5.28 ± 2.67	0.760 ± 0.120
WOMAC-function overall	1347	6.07 ± 14.56	0.790 ± 0.120	312	3.65 ± 8.33	0.800 ± 0.120
No function limitation (score = 0)	737	–	0.820 ± 0.110	188	–	0.810 ± 0.110
Moderate function limitation (score ≤ 17)	475	5.67 ± 4.69	0.790 ± 0.120	105	5.41 ± 4.18	0.780 ± 0.120
Severe function limitation (score > 17)	135	40.61 ± 25.44	0.740 ± 0.130	19	30.05 ± 14.36	0.770 ± 0.130

CDAH childhood determinants of adult health, *HSU* health state utility, *n* number of patients at the respective time point, *SD* standard deviation, *WOMAC* Western Ontario MacMaster osteoarthritis score

Table 3 Cross-sectional association between WOMAC symptoms and health state utility value

	Unadjusted		Adjusted for age and sex	Adjusted for Age, sex, and BMI	Adjusted for age, sex, BMI, education
	n (%)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)
Total WOMAC overall (0–120)	1309 (83.54)	− 0.001 (− 0.0015 to − 0.0009)	− 0.001 (− 0.0015 to − 0.0010)	− 0.001 (− 0.0015 to − 0.0009)	− 0.001 (− 0.0014 to − 0.0009)
None (score = 0)	569 (36.31)	Ref			
Moderate (score 1–24)	570 (36.38)	− 0.019 (− 0.0321 to − 0.0067)	− 0.019 (− 0.0326 to − 0.0072)	− 0.018 (− 0.0310 to − 0.0055)	− 0.018 (− 0.0305 to − 0.0050)
Severe (score > 24)	170 (10.85)	− 0.078 (− 0.0986 to − 0.0580)	− 0.080 (− 0.1004 to − 0.0597)	− 0.075 (− 0.0966 to − 0.0552)	− 0.074 (− 0.0945 to − 0.0531)
Linear trend		**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
WOMAC-pain overall (0–25)	1310 (83.60)	− 0.005 (− 0.0057 to − 0.0035)	− 0.005 (− 0.0058 to − 0.0035)	− 0.005 (− 0.0058 to − 0.0035)	− 0.004 (− 0.0057 to − 0.0033)
No pain (score = 0)	740 (47.22)	Ref			
Moderate pain (1–5)	366 (23.36)	− 0.022 (− 0.0364 to − 0.0086)	− 0.023 (− 0.0368 to − 0.0090)	− 0.022 (− 0.0356 to − 0.0078)	− 0.022 (− 0.0354 to − 0.0076)
Severe pain (score > 5)	204 (13.02)	− 0.066 (− 0.0841 to − 0.0476)	− 0.067 (− 0.0850 to − 0.0485)	− 0.063 (− 0.0812 to − 0.0441)	− 0.060 (− 0.0780 to − 0.0410)
Linear trend		**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
WOMAC-stiffness overall (0–10)	1310 (83.60)	− 0.007 (− 0.0097 to − 0.0052)	− 0.008 (− 0.0099 to − 0.0054)	− 0.007 (− 0.0093 to − 0.0047)	− 0.007 (− 0.0090 to − 0.0044)
No stiffness (score = 0)	818 (52.20)	Ref			
Moderate (1–2)	225 (14.36)	− 0.012 (− 0.0287 to 0.0044)	− 0.013 (− 0.0293 to 0.0037)	− 0.012 (− 0.0282 to 0.0048)	− 0.011 (− 0.0274 to 0.0056)
Severe (score > 2)	267 (17.03)	− 0.042 (− 0.0577 to − 0.0256)	− 0.043 (− 0.0590 to − 0.0268)	− 0.039 (− 0.0549 to − 0.0226)	− 0.036 (− 0.0518 to − 0.0196)
Linear trend		**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
WOMAC-function overall (0–85)	1315 (83.92)	− 0.002 (− 0.0022 to − 0.0014)	− 0.002 (− 0.0022 to − 0.0014)	− 0.002 (− 0.0021 to − 0.0013)	− 0.002 (− 0.0021 to − 0.0013)
No function limitation (score = 0)	716 (45.70)	Ref			
Moderate function limitation (1–17)	464 (29.61)	− 0.026 (− 0.0385 to − 0.0125)	− 0.026 (− 0.0386 to − 0.0127)	− 0.023 (− 0.0368 to − 0.0108)	− 0.023 (− 0.0362 to − 0.0103)
Severe function limitation (score > 17)	135 (8.62)	− 0.076 (− 0.0976 to − 0.0535)	− 0.077 (− 0.0995 to − 0.0553)	− 0.074 (− 0.0961 to − 0.0514)	− 0.071 (− 0.0938 to − 0.0491)
Linear trend		**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**

Bold denotes statistical significance, $p < 0.05$

BMI body mass index, *CI* confidence interval, *HSU* health state utility, *n* number of patients at the respective time point, *WOMAC* Western Ontario MacMaster osteoarthritis score

increased knee pain compared to those with stable knee pain had a statistically and clinically significant negative impact on HSU at the end of follow-up at CDAH-3 [adjusted regression coefficient = − 0.040 (− 0.073 to − 0.008; $p = 0.015$)] (Table 4).

The change in WOMAC scores over 6–9 from CDAH-knee to CDAH-3 was also negatively associated with a change in HSU value during the same period, although not statistically significant (Online Appendix 1, Table 2). Similarly, WOMAC at CDAH-knee was negatively associated with a change in HSU from CDAH-knee to CDAH-3 follow-up.

Sub-group analysis

Sub-group analysis of cross-sectional data based on sex showed a consistently stronger effect of reduced WOMAC scores on HSU decrement in women compared to men across the WOMAC symptom severity groups for all WOMAC domains, except WOMAC-function (Online Appendix 1, Table 3). Similarly, younger participants (36–40 years) had consistently more substantial effects of worse WOMAC scores on HSU decrement compared to older participants in the age groups of 41–45 years, and ≥ 45 years, across the WOMAC symptom severity groups for various WOMAC domains (Online Appendix 1, Table 4). No specific pattern

Table 4 Longitudinal association of WOMAC symptoms over 6–9 years with health state utility at CDAH3

Outcome: HSU at CDAH3	Unadjusted		Adjusted for age and sex
	n	Coef. (95% CI) *p* value	Coef. (95% CI) *p* value
Predictor: total-WOMAC score at CDAH-knee	307	**− 0.002 (− 0.0027 to − 0.0006)** ***p* < 0.0001**	**− 0.002 (− 0.0027 to − 0.0007)** ***p* < 0.0001**
Predictor: Sum of total-WOMAC score at CDAH-knee and CDAH3	214	**− 0.001 (− 0.0019 to − 0.0005)** ***p* < 0.0001**	**− 0.001 (− 0.0020 to − 0.0006)** ***p* < 0.0001**
Predictor: total-WOMAC scored increased vs stable	214	− 0.023 (− 0.0558 to 0.0087) *p* = 0.152	− 0.026 (− 0.0578 to 0.0064) *p* = 0.116
Predictor: WOMAC-pain score at CDAH-knee	307	**− 0.004 (− 0.0081 to − 0.0001)** ***p* = 0.042**	**− 0.004 (− 0.0081 to − 0.0002)** ***p* = 0.038**
Predictor: Sum of WOMAC-pain score at CDAH-knee and CDAH3	215	**− 0.003 (− 0.0061 to − 0.0008)** ***p* = 0.011**	**− 0.003 (− 0.0061 to − 0.0008)** ***p* = 0.012**
Predictor: WOMAC-pain score increased vs stable	215	**− 0.038 (− 0.0710 to − 0.0055)** ***p* = 0.022**	**− 0.040 (− 0.0730 to − 0.0079)** ***p* = 0.015**
Predictor: WOMAC-stiffness score at CDAH-knee	307	**− 0.011 (− 0.0175 to − 0.0054)** ***p* < 0.0001**	**− 0.012 (− 0.0184 to − 0.0064)** ***p* < 0.0001**
Predictor: Sum of WOMAC-stiffness score at CDAH-knee and CDAH3	217	**− 0.009 (− 0.0140 to − 0.0051)** ***p* < 0.0001**	**− 0.011 (− 0.0153 to − 0.0064)** ***p* < 0.0001**
Predictor: WOMAC-stiffness score increased vs stable	217	− 0.019 (− 0.0534 to 0.0159) *p* = 0.287	− 0.022 (− 0.0570 to 0.0122) *p* = 0.204
Predictor: WOMAC-function score at CDAH-knee	307	**− 0.002 (− 0.0040 to − 0.0009)** ***p* = 0.002**	**− 0.002 (− 0.0040 to − 0.0009)** ***p* = 0.002**
Predictor: Sum of WOMAC-function score at CDAH-knee and CDAH3	216	**− 0.001 (− 0.0028 to − 0.0007)** ***p* < 0.0001**	**− 0.002 (− 0.0029 to − 0.0008)** ***p* < 0.0001**
Predictor: WOMAC-function score increased vs stable	216	− 0.022 (− 0.0561 to 0.0110) *p* = 0.186	− 0.027 (− 0.0603 to 0.0065) *p* = 0.114

Bold denotes statistical significance, $p < 0.05$

WOMAC stable includes both WOMAC stable and WOMAC decreased

CI confidence interval, *HSUs* health state utility, *n* number of patients at the respective time point, *WOMAC* Western Ontario MacMaster osteoarthritis score

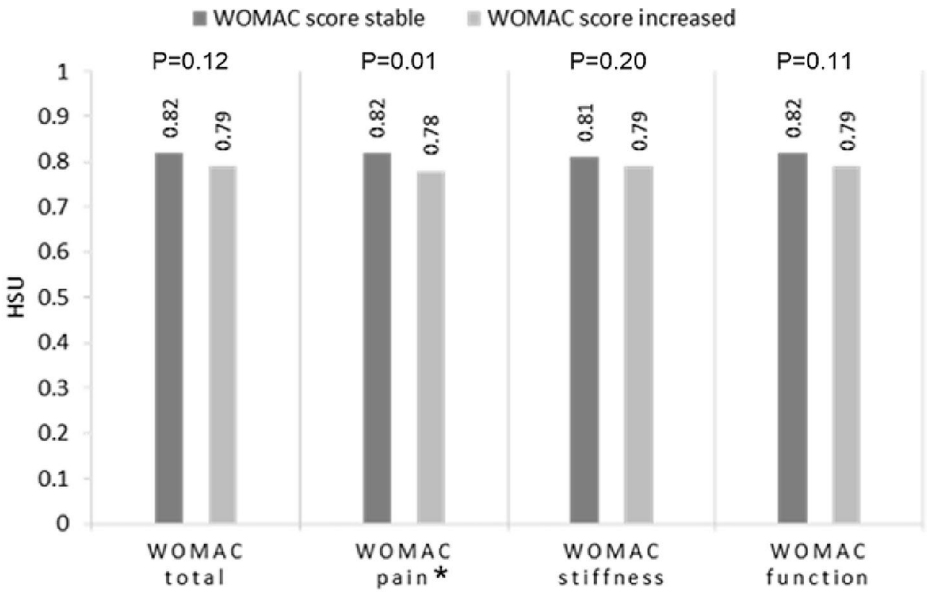


Fig. 2 Longitudinal association of HSU with a change in WOMAC score

P-value as per regression analysis; * Statistically significant
HSU, health state utility; WOMAC, Western Ontario MacMaster osteoarthritis score

was observed for the sub-group analysis based on BMI (Online Appendix 1, Table 5).

Discussion

To our knowledge, this is the first study examining both the cross-sectional and longitudinal relationship between knee symptoms (pain, stiffness, and dysfunction) and HRQoL assessed with SF-6D HSUs in middle-aged adults. In this population-based cohort of Australian middle-aged adults that is broadly representative of a middle-aged Australian population, we found that WOMAC knee symptoms scores were negatively associated with HSU, and an increase in knee pain over 6–9 years was associated with a reduction of HSU as compared to those with no or stable knee pain [64]. We also found that the SF-6D had good discriminatory power for the middle-aged adult cohort, particularly when we examined the decrements for disease-severity classifications.

It is crucial to consider the public health implications of knee pain in a younger (middle-aged) population. Previous studies have shown that the reduction in HRQoL due to knee pain leads to reduced productivity [65–67]. However, there has been less focus on knee pain in the relatively younger population [2]. Therefore, our novel findings and the SF-6D decrements associated with diminished knee health across disease-severity classifications can be used to populate health economic models. Additionally, our HSU findings could also be adopted as baseline measures for clinical assessment and comparisons.

Health economics modelling of a middle-aged cohort's knee health

Our study addresses an important evidence gap in the literature by providing HSUs associated with knee pain and symptoms for a younger population cohort where treatments or interventions (particularly for severe disease severity, or to avoid increased disease severity) are of humanistic and economic interest to the individual, health payers, and broader society. We suggest that our large Australian sample of middle-aged people with knee pain is a largely representative of middle-aged knee cohorts who suffer knee pain in other jurisdictions [64]. Therefore, an important application of our results would be as a baseline value in an economic evaluation assessing health economic and humanistic burden of knee pain and knee OA for health technology assessment [10, 68]. For instance, in patients with knee OA, to assess the benefits of a treatment alleviating pain, researchers need the average HSU for a cohort that has knee OA (and its associated knee pain) and the average HSU for a cohort that does not have knee OA but may have underlying knee pain (i.e., the baseline) [69–71]. Consequently, in a health economic evaluation of treatment for knee OA assigning an HSU value of '1' for the starting health state of a patient with no knee OA associated pain may not correctly capture the state and is likely to overestimate the effect of the intervention [70–72]. The mean HSUs corresponding to the various knee symptoms (knee pain, stiffness, function, and total-WOMAC) categories (no symptom, moderate, and severe symptoms and the associated utility decrement) and the regression coefficient can inform cost-effectiveness analyses of knee pain and knee OA [68, 73]. For example, our result provides HSUs that can be appropriately used in economic evaluations, such as the investigation conducted by Karmarkar et al., as a baseline value [32]. Similarly, for studies assessing the humanistic burden of knee OA, assigning a baseline HSU value and the longitudinal change in the HSU over the years, for those who do not develop knee OA, based on our data will help in the realistic estimation of the humanistic burden over the life course [32, 74, 75]. Hence, the use of baseline HSU and change in HSU from our study is likely to represent a more accurate prediction of health state trajectory than assuming an HSU of '1' for the individuals without knee OA [32, 74].

SF-6D discriminatory power for a middle-aged cohort's knee health

Another key finding of our study was the validation of the discriminatory power of the SF-6D multi-attribute utility instrument' for a younger knee health cohort. The choice of the correct multi-attribute utility instrument that has discriminatory power to assess health states and the changes across health states is crucial [56]. Our study has shown that as knee health diminishes from normal to severe, the SF-6D's HSU decrease was clinically meaningful.

Consistent with our findings for the SF-6D, earlier studies using *older age cohorts* have compared the association of knee pain with HRQoL in patients with established knee OA [8]. In two population-based cohort studies, Muraki et al., using the SF-8D and EQ-5D-3L, reported that knee pain was associated with reduced quality of life in both men and women [2, 76]. Using the SF-36 score only (not SF-6D HSUs), Antonopoulou et al. reported the detrimental effect of knee pain on quality of life for patients with musculoskeletal disorders attending the primary care center [77]. Similarly, longitudinal studies have reported that worsening of knee pain is one of the significant factors associated with reduced quality of life (assessed using KOOS, Japanese Knee Osteoarthritis Measure, and SF-12) in patients with knee OA [42, 78, 79]. In patients with knee OA, knee pain is shown to cause avoidance of physical activity and leading to muscle weakness and disability [80]. Similarly, knee pain in young adults can affect various aspects of daily life activity and hence impacting overall HRQoL [81, 82]. Several

factors may be impacting HRQoL in this population; however, in our study, the multivariate analysis adjustment with BMI, education, and co-morbidity did not markedly alter the estimated coefficients of the covariates. The effect of BMI on HSU was not significant, with the standardized linear regression coefficients of − 0.07 as compared to − 0.24 for the total-WOMAC, which may be the reason that BMI did not impact our study's estimates. Hence, our interpretation is based on estimates adjusted for age and sex only, although we also presented data on other adjustments.

Regarding comparisons with both the UK and Australian population norms for a middle-aged cohort, our HSU values for participants who reported severe knee health were diminished from both the UK and Australian population norms by the MCID (reduced by 0.05 utility points) for the 45–49 year (UK) and 31–40 year (Australia) age category of population norms (0.79 utility points) [62]. Nevertheless, we also note that the overall mean HSU values in our study correspond to the previously reported population norm for both countries [62]. The pattern of differences in HSU between sex, with female reporting lower HSU, was also consistent with previously reported values from both the UK and the Australian population [62]. Previous studies have cited sociodemographic and socioeconomic differentials as a possible explanation for the sex differences in HRQoL [83, 84].

Strengths and limitations

The strengths of our study included assessment of cross-sectional and longitudinal association using 6–9 year follow-up data from a population-based cohort of Australian middle-aged adults. The large cross-sectional sample enabled the statistical power to examine the association of knee-symptom severity and the HSU. This is important as the younger population is less likely studied in relation to joint pain and HRQoL. We also suggest that this large Australian sample of middle-aged people with knee pain is broadly representative of middle-aged knee cohorts who suffer knee pain in other jurisdictions. Second, we used the disease-specific HRQoL (WOMAC scale) instrument to classify knee pain to enable us to assess the discriminatory sensitivity of the SF-6D. Third, using the SF-6D, we generated baseline HSUs from a large representative cohort of a middle-aged population.

Our study also has certain limitations to be considered while interpreting the findings. We categorized the WOMAC score into subgroups based on the severity of symptoms to allow easy interpretation of the results. Similar approaches have been used by other researchers earlier [53–55]. While we argue that these subgroups may be useful for health economic analyses (such as studies may subgroup patients based on knee-symptom severity and corresponding HSU), some information is lost when continuous measures are converted to categorical subgroups. Although this approach may have limited some information and statistical power, it improved the clinical interpretation and applicability of findings. We also acknowledge that we used the UK value set for this study; however, this is the most comparable value set that can be derived using the SF-12 variant of the SF-6D algorithm, and we have assumed that the derived value set is broadly comparable to the Australian middle-aged cohort for knee health. Another limitation of our study is that there is no MID or MCID for knee pain for the SF-6D tariff generated from the patient-reported responses to SF-12 questionnaire. Nevertheless, there are some studies that have estimated a composite or knee OA MID or MCID for the SF-36 variant of the SF-6D algorithm and we subsequently adopted a conservative estimate of 0.04 utility points for our study. We note that there is one study that investigated rheumatoid arthritis of the hand that used the SF-12 variant for SF-6D and this study estimated a benefit at 4 and 12 months of 0.06 utility points. A final limitation is that there are no Australian population norms for the SF-12 SF-6D algorithm. Therefore, to examine general trends and to provide further contextualisation to our study we also considered the population norms for both the UK and Australia which are similar for the general population and for the middle-aged cohorts.

Conclusion

In a middle-aged population-based sample, WOMAC scores and increasing WOMAC scores over 6–9 years for knee pain were negatively associated with HSUs, including clinically meaningful differences in SF-6D HSUs from normal to moderate/severe knee symptoms. Our findings may be used by decision-makers to define a more realistic and conservative baseline and ongoing HSU values when assessing QALY changes associated with OA interventions. Our findings also validate the discriminatory power of the SF-6D for assessing knee health for a middle-aged cohort.

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Author contributions AS, BA, and AP conceived the Study. AS, JC, and LB conceived the present analysis. AS and LB cleaned and prepared the data and performed the analysis. AS and JC undertook HSU estimation using the algorithm. AS drafted the first draft of the manuscript, and JC, AV, GJ, LB, AP TD, FC, CD, and BA edited the manuscript. All authors commented on and approved the final version of the manuscript.

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Declarations

Conflict of interest All authors declare that there is no conflict of interest.

Ethical approval The Southern Tasmania Health and Medical Human Research Ethics Committee, Monash University Human Research Ethics Committee, and the Northern Sydney and Central Coast Area Human Research Ethics Committee provided ethical approval for the study (Ethics ID: H0018491).

Informed consent Participants were asked to read the participant information and to consent before entering the study.

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