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Long-term mortality and causes of death among patients with a total knee prosthesis in primary osteoarthritis

Tuomo Visuri [a,*], Keijo Mäkelä [b], Pekka Pulkkinen [a], Mia Artama [c], Eero Pukkala [c,d]

[a] Department of Public Health, University of Helsinki, P.O. Box 40, FI-00140, Finland
[b] Department of Orthopedics and Traumatology, University of Turku, FI-20014, Finland
[c] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Unioninkatu 22, FI 00130 Helsinki, Finland
[d] School of Health Sciences, University of Tampere, FI-33014, Finland

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ABSTRACT

Background: Short and midterm mortality of patients with osteoarthritis (OA) who have undergone total knee arthroplasty (TKA) is generally lower than that of the general population. Due to an increasing number of young patients who undergo TKA the expected lifetime of these patients is increasing. The purpose of this study was to assess the causes of death and long-term mortality among Finnish TKA patients.
Methods: Standardized mortality ratios (SMRs) for total and site specific causes of death were calculated for 9443 TKA patients operated on in 1980 to 1996 for OA and followed until 2012.
Results: The mean follow-up time was 14 years (maximum 33 years). During follow-up, 77% of the patients had died. The all-cause SMR was 1.00. It was significantly lower than in the reference population (SMR 0.73) during the first 10 years after operation, but higher during the next 10 years (SMR 1.23), and even more after 20 years (SMR 1.95). The SMR for cardiovascular mortality was 1.03 and accounted for 52% of all deaths. Significant excess mortality was observed in diseases of the digestive tract (SMR 1.29). Deaths due to cardiovascular diseases, Alzheimer's disease and dementia comprised 68% of all deaths that took place 10 years or later after TKA.
Conclusions: The mortality of TKA patients with OA is significantly reduced during the first 10 postoperative years but exceeds the mortality of the general population after that. This trend should be taken into account when young patients undergo a TKA.
Level of evidence: Observational study, III.

1. Introduction

Mid-term mortality of patients with total knee arthroplasty (TKA) for primary osteoarthritis (OA) in previous single and multicenter studies has been reported to be the same [1], lower [2–4] or even higher [5] than that of the general population. In a large US Medicare cohort the hazard ratio for mortality of TKA patients at seven years compared with matched knee OA patients who have not undergone a TKA was significantly reduced [6].

Results from the Swedish Knee Arthroplasty Register show that the OA TKA patients have a reduced overall mortality during the first 12 post-operative years, after which it increases and become significantly higher than in the general population. This increase was especially strongly associated with patients younger than 55 years. Cardiovascular, gastrointestinal, and urogenital diseases were largely responsible for the higher mortality. The authors proposed that there may be a link between early onset of knee OA and increased mortality [7].

There is growing evidence that OA is associated with cardiovascular diseases (CVDs) [8–10] which may relate to the long-term mortality of TKA patients. Patients with radiologically verified OA of the hip or knee have an increased risk of all cause mortality when followed up for a median of 13 to 14 years [10,11].

TKA is essential for the treatment of severe pain and for the restitution of walking ability. The mortality of patients with OA of the knee undergoing TKA may not exceed that of the general population, but this consideration is hampered by the fact that the long-term impact of TKA on all cause and disease specific mortality is not well known. The purpose of this study of a Register was to assess how all disease and main disease group specific late mortality deviates from those of the general population over a long period of time.

2. Patients, materials and methods

The patient data were obtained from the Finnish Arthroplasty Register covering the years 1980 to 1996. The dates and causes of death of the cohort subjects were retrieved from Statistics Finland by record linkage using the individual's personal identity code as the key. The coverage of the cause-of-death statistics is virtually complete.

* Corresponding author at: Takojantie 1B, 02130 Espoo, Finland. Tel.: +358 40 5281316.
E-mail address: tuomo.visuri@helsinki.fi (T. Visuri).

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Table 1
Numbers of patients (n) with total knee arthroplasty by sex and age at operation and number of person-years at risk up to the end of 2012.

Age (years)	Men		Women		All	
	n	Person-years	n	Person-years	n	Person years
30 to 39	6	22	6	14	12	36
40 to 49	37	177	47	226	84	403
50 to 59	221	1134	528	2307	749	3441
60 to 69	787	5405	2801	16,613	3589	22,018
70 to 79	821	11,100	3572	46,173	4393	57,273
≥80	129	7242	488	41,294	617	48,536
Total	2001	25,080	7443	106,628	9443	131,708

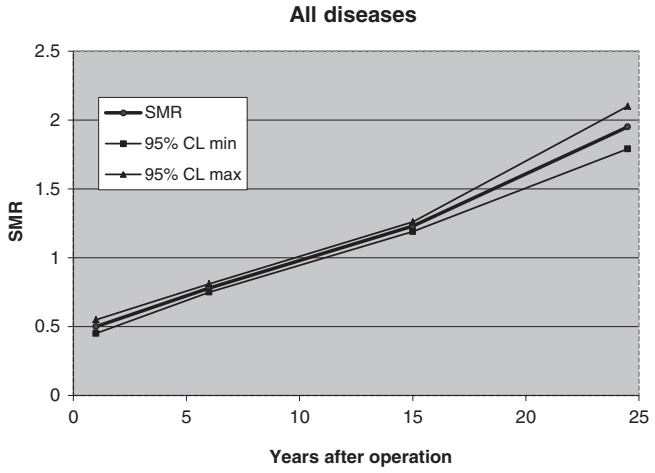

Fig. 1. Standardized mortality ratios (SMRs) with 95% confidence limits for all diseases during 25 years of follow-up among 9443 patients with a total knee arthroplasty for osteoarthritis.

Only patients who had undergone primary TKA and who were operated on for OA were included in the final analysis. The follow-up of the patients started from the first primary TKA. Mortality risk related to later revisions were not studied separately. The patient data have been described in detail previously [12]. All patients had received an unconstrained TKA, 79% had cobalt chromium molybdenum and 21% titanium aluminium vanadinium alloy parts. The percentage of cemented component fixation on the femoral side was 46 and on the tibial side 57.

The standardized mortality ratio (SMR) was expressed as the ratio of observed and expected number of cases. The expected numbers of deaths were calculated by multiplying the number of person-years in each stratum by the corresponding average mortality rate throughout Finland during the period of observation. The number of observed cases for each cause of death and person-year during the follow-up was stratified by gender, calendar period, five year age group, and the follow-up time since the TKA operation. The calendar periods were 1980 to 1985, 1986 to 1991, 1992 to 1997, 1998 to 2002, 2003 to 2007, and 2008 to 2012. The closing date was December 31, 2012. The follow-up categories were <1, 1 to 9.99, 10 to 19.99, and ≥20 years since the operation. The 95% confidence intervals (95% CIs) were defined assuming that the number of observed cases followed a Poisson distribution.

The list of causes of death based on International Classification of Diseases (ICD) versions: ICD-8, ICD-9, and ICD-10. Of the main categories cancer, cardiovascular disease (CVD), respiratory, genitourinary, digestive system, dementia, Alzheimer's disease, and accidental deaths were analyzed. This study was approved by the National Institute for Health and Welfare, decision THL/1615/5.05.00/2013. The study subjects were not contacted and therefore no informed consents were required according to the Finnish regulations.

3. Results

Total number of person-years was 131,708 and 79% of the patients were females (Table 1). A total of 7254 (77%) of the TKA patients had died by the closing date. The mean follow-up time was 14 years (Table 1).

All-cause mortality was significantly reduced during the first 10-year follow-up period, but it was significantly increased during the second follow-up decade and reached the level of mortality of the normal population by 11 years. After 20 years of follow-up, the mortality of the study group exceeded significantly the mortality of the normal population (Fig. 1, Table 5). There were 1020 fewer deaths than expected during the first decade of follow-up, and an excess of 1005 cases after that period (Table 3). Females and males had similar SMRs throughout the follow-up period (Table 2).

Overall cancer mortality was significantly reduced but showed an increasing trend over time and reached the mortality of the normal population by the 17th postoperative year (Fig. 2, Table 3). Cancer deaths were reduced by 16.3% during the first 10 year period and by 1.0% after that (Table 3).

Respiratory tract cancer mortality was especially low: the SMR of all patients was 0.68 (95% CI 0.57 to 0.81); 0.61 (95% CI 0.46 to 0.78) for males and 0.78 (95% CI 0.59 to 0.99) for females. Mortalities from colon, breast and cervical and uterine cancer were significantly decreased as well. Late mortality in prostate and hematopoietic cancers was similar with that of the average population.

Cardiovascular disease was the most common cause of death and mortality increased linearly during the whole follow-up time. It reached the level of the normal population by the 10th postoperative year and remained higher than for the general population during the remaining follow-up time (Fig. 3, Table 5). Cardiovascular disease accounted for 52% of all causes of death. During the first 10 years there was a 40.2% reduction from the expected value, but after that cardiovascular deaths comprised 631 numerical excess deaths, which is 62.8% of all numerical excess deaths (Table 3). Men and women presented with a similar trend of CVD mortality: the SMRs during the first postoperative year were 0.61 and 0.52, from two to nine years 0.86 and 0.76, from 10 to 19 years 1.37 and 1.30, and after 20 years 1.68 and 2.06, respectively.

Mortality in respiratory diseases was lower during the first 10 years (Tables 4 to 5), after which it was in accordance with the general population both for males and females.

Mortality from Alzheimer's disease and dementia was also significantly lower during the first 10 years after surgery, after which it showed a steep increase (Tables 4 to 5). There was a significant excess of deaths in these diseases among females (SMR 1.56, 95% CI 1.27 to 1.87) but not among males (SMR 0.96, 95% CI 0.79 to 1.14). This group of diseases was the second highest cause of death with 18.7% after 10 years with a numerical excess of 43.5 deaths (Table 3).

A similar trend was observed concerning the mortality due to genitourinary and digestive tract diseases. The mortality in digestive tract diseases was significantly increased (SMR 1.29) (Tables 4 to 5). The incidence of accidental deaths was in line with the normal population (Tables 4 to 5). There was, however, a numerical excess of 16.6 deaths after the 20th postoperative year (Table 3).

Table 2
Observed number of total deaths (Obs), standardized mortality ratio (SMR) 95% confidence interval (95% CI) among 9443 patients with total knee arthroplasty for osteoarthritis by gender and number of postoperative years.

Time since TKA surgery (completed years)	Men		Women		All patients	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
0–1	96	0.50 (0.41–0.61***)	218	0.50 (0.44–0.56***)	314	0.50 (0.45–0.55***)
2–9	680	0.84 (0.78–0.90***)	1822	0.77 (0.73–0.80***)	2502	0.78 (0.75–0.81***)
10–19	758	1.22 (1.13–1.30***)	3098	1.23 (1.19–1.27***)	3856	1.23 (1.19–1.26***)
20+	79	1.65 (1.31–2.05***)	503	2.00 (1.83–2.17***)	582	1.95 (1.79–2.11***)
Total	1613	0.97 (0.92–1.01)	5641	1.01 (0.98–1.03)	7254	1.00 (0.98–1.02)

*** $p < 0.001$.

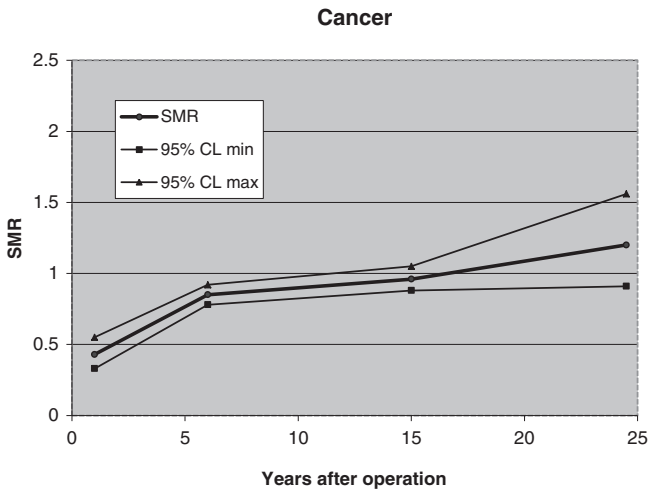

Fig. 2. Standardized mortality ratios (SMRs) with 95% confidence limits for cancer during 25 years of follow-up among 9443 patients with total knee arthroplasty for osteoarthritis.

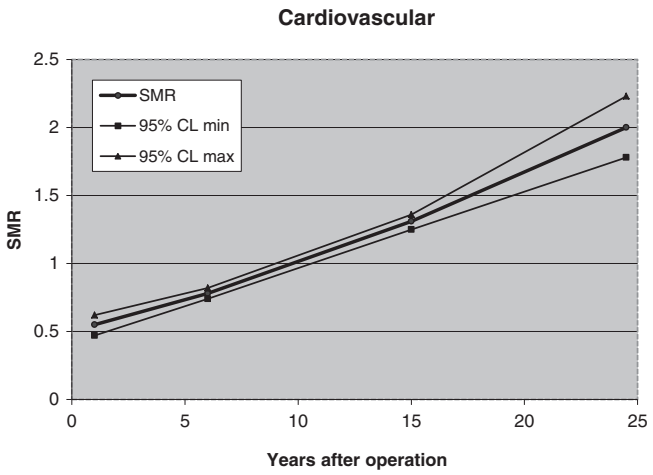

Fig. 3. Standardized mortality ratios (SMRs) with 95% confidence limits for cardiovascular disease during 25 years of follow-up among 9443 patients with total knee arthroplasty for osteoarthritis.

4. Discussion

Total knee arthroplasty is usually indicated for patients with end-stage OA which causes severe pain and a compromised walking ability. Knee OA as such is associated with increased mortality. There is data, derived from population-based epidemiologic and clinical studies, which provide some evidence that radiographic and symptomatic OA, particularly of the knees, is associated with increased mortality related especially to acute CVD and gastrointestinal causes [8]. Hip and knee OA patients with moderate symptoms after a median of 13 to 14 years follow-up have been shown to have significantly increased all-cause mortality related to the severity of the walking disability [10,11]. Restricted walking before the TKA (inability to walk or ability to walk only indoors) is a strong predictor of postoperative mid-term mortality among patients above the age of 75 [13].

Due to surgical stress, the postoperative mortality of total joint arthroplasty (TJA) patients increases during the first 22 to 41 days after surgery [14]. This excess changes rapidly to a reduced risk of mortality. The mortality ratio during the first postoperative year in our study was also only half of the expected population value. This reduction pertained to almost all disease related groups for the next 10 years. The "healthy patient" effect, i.e. preoperative selection of the patients has generally been regarded as a cause for this phenomena. The "healthy patient" effect is undefined and its duration is not known. There may be several reasons for this reduction. TKA may have a cardioprotective effect due to improved cardiovascular fitness [15]. Ravi et al. studied a propensity score matched cohort of 153 matched pairs of participants with moderate or severe OA. Over a median follow-up period of seven years, TJA (94 TKA, 49 total hip arthroplasty (THA)) was associated with a significantly reduced rate of CVD events compared to matched controls; for TKA patients the hazard ratio was 0.46 (0.29 to 0.75) [16]. Furthermore, the reduction in chronic pain may be another reason why mortality rates decrease in the first 10 years after TKA.

Both pre- and postoperatively TKA patients undergo a dental examination and dental treatment to prevent hematogenous dissemination of oral biofilm bacteria to the prosthesis and possible infection. Periodontitis imparts an increased risk of future CVD [17]. Patients who receive knee implants are also likely to be under increased medical surveillance in general and started on medication for CVDs. The protective effect of medication may, at least partly, explain the reduction in mortality. The role of each factor requires further studies.

The growing mortality of the TKA patients after 10 years of follow-up starts to exceed the gain of lifetime seen before that period. Reasons for the excess mortality after 10 years are not known. Walking disability might be a common denominator for these phenomena. It predicts mortality among knee OA patients [10,11], preoperatively [13], and even postoperatively as shown by Lizaur-Utrilla in a 10 years follow-up study [4]. Deterioration of the walking capacity of TKA patients after 10 years has not been studied. However the subjective outcomes of TKA patients during the first ten years of surgery were worse than the objective outcomes. Rat et al. studied the quality of life among OA TJA patients three and 10 years after surgery and observed that scores for pain, mental health, and social dimensions were lower than for the

Table 3
Observed (Obs) vs. expected (Exp) deaths before and after 10 years of TKA surgery among 9443 patients with total knee prosthesis for osteoarthritis.

Cause of death	Time since TKA surgery					
	<10 years			≥10 years		
	Obs	Exp	Obs–Exp	Obs	Exp	Obs–Exp
Cancer	555	720.7	−165.7	523	533.3	−10.3
Cardiovascular	1453	1862.9	−409.9	2339	1708.1	+630.9
Respiratory	167	316.2	−149.1	236	263.4	+11.3
Alzheimer, dementia	162	306.2	−144.2	700	512.3	+187.7
Genitourinary	34	52.1	−18.1	77	46.9	+30.1
Digestive organs	119	120.4	−1.4	177	108.4	+68.7
Accidents, violence	119	126.1	−7.1	137	113.3	+23.7
All causes	2816	3835.7	−1019.7	4438	3433.5	+1004.6

Table 4
Observed number of deaths (Obs), standardized mortality ratio (SMR) and 95% confidence interval (95% CI) among 9443 patients with total knee prosthesis for osteoarthritis in the main disease groups.

Cause of death	TKA patients		
	Obs	SMR	95% CI
Cancer	1078	0.86	0.81–0.91***
Cardiovascular	3792	1.03	1.00–1.06*
Respiratory	403	0.75	0.67–0.82***
Alzheimer, dementia	862	1.06	0.99–1.13
Genitourinary	111	1.12	0.92–1.33
Digestive system	296	1.29	1.15–1.44***
Accidents and violence	234	1.10	0.97–1.25
All causes	7254	1.00	0.98–1.02

* $p < 0.05$.
*** $p < 0.001$.

Table 5
Observed number of deaths (Obs) and standardized mortality ratio (SMR) with 95% confidence intervals (95% CI) among 9443 patients with total knee prosthesis for osteoarthritis in the main disease groups by the completed follow-up time.

Cause of death	Time since TKA surgery (completed years)											
	0–1			2–9			10–19			≥20		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
Cancer	59	0.43	0.33–0.55***	496	0.85	0.78–0.92***	468	0.96	0.88–1.05	55	1.20	0.91–1.56
Cardiovascular	180	0.78	0.74–0.82***	1273	0.78	0.74–0.82***	2045	1.31	1.25–1.36***	294	2.00	1.78–2.23***
Respiratory	10	0.22	0.11–0.40***	157	0.58	0.49–0.67***	215	1.02	0.89–1.16	21	1.51	0.94–2.31
Alzheimer, dementia	1	0.03	0.00–0.18***	161	0.59	0.51–0.68***	570	1.24	1.14–1.34***	130	2.47	2.07–2.91***
Genitourinary	4	0.50	0.14–1.28	30	0.68	0.46–0.96*	64	1.48	1.14–1.88**	13	3.56	1.90–6.09***
Digestive system	12	0.65	0.34–1.13	107	1.05	0.86–1.25	159	1.60	1.36–1.86***	18	2.01	1.19–3.17*
Accidents and violence	22	1.01	0.63–1.53	97	0.93	0.76–1.13	118	1.14	0.94–1.34	19	1.94	1.17–3.02*
All causes	314	0.50	0.45–0.55***	2502	0.78	0.75–0.81***	3856	1.23	1.19–1.26***	582	1.95	1.79–2.10***

* $p < 0.05$.
*** $p < 0.001$.

reference population at the 10-year follow-up [18]. Self reported function and pain of TKA patients had worsened at 10 years compared to their situation at two years [19].

A similar mortality pattern has been observed among OA patients who have undergone conventional metal-on-polyethylene THA: the SMR increased from 0.37 during the first postoperative year to 1.38 by 20 years [20].

In contrast to the time trend of other disease groups, cancer deaths increased only slightly during the whole follow-up time. Meta-analyses show that after a mean of 4.5 to 5.1 years, the overall standardized cancer ratio (SIR) or cancer among TKA patients with OA is 0.94 and among patients operated on for all indications 0.97 [21,22]. In our cohort the SIR at a mean of 5.5 years of follow-up was 0.98. The SIRs of hematopoietic cancers (1.26) and of prostatic cancer (1.48) were increased [12], but after longer follow-up time mortality in these diseases was in line with the general population. Although results based on cancer incidence and cancer-related mortality are not totally comparable, SMRs observed in this study and SIRs published earlier from the same cohort [12] with 80,000 less person-years, confirm that TKA does not carry any significantly increased overall cancer risk.

The incidence of respiratory tract cancer was lower in this study than has been previously published [12]. Heavy tobacco smoking was associated with a decreased risk of knee OA in a comparison with never-smoking (OR 0.2; 95% CI 0.1 to 0.5) [23]. A large register study showed an independent inverse association between smoking and the risk of receiving a TJA. Male smokers were 30% less likely and female smoker 40% less likely than never smokers to undergo TJA surgery [24]. Smoking seems to have a preventive effect on the development of OA. It has been suggested that activation of α7 nicotinic acetylcholine receptors prevents monosodium iodoacetate-induced OA in rats [25]. However, it might as well be that smokers just do not go to the doctor as much as non-smokers. Presumed small number of smokers in our cohort may, in fact, explain the low mortality rate in respiratory and perhaps other diseases, as well.

Cardiovascular disease was the main cause of death and reason for the increased mortality after 20 years. OA and CVDs share common risk factors. In a cohort of 23,570 patients cardiovascular risk factors were linked with registers of OA-related arthroplasty data. The risk ratio was significantly associated with the severity of CVD from the second lowest to the highest disease severity quartile [9]. A large prospective and 10-years longitudinal study showed that OA was an independent predictor of CVD compared with age and sex matched individuals especially among older men and younger and older women. The risk was elevated by 26% among individuals who underwent total joint replacement [26]. Self- reported prevalence of OA was 35.3% in the US national health survey from 1999 to 2008 and they had higher odds for CVDs (OR 1.53) compared with subjects without OA [27]. After median of 14.4 follow-up years Hoeven et al. concluded that the patients aged 55 years and older with knee OA had not an increased risk of CVD but there was a close relationship with their disability and OA [28]. After median of 14 years follow-up, 1163 patients with hip or knee OA had an excess of all-cause mortality compared with the general population. Particularly CVDs were associated with excess mortality (SMR 1.71). Mortality was related to increasing age, male sex, self-reported history of diabetes, cancer, CVD and walking disability; the more severe the walking disability, the higher risk of death [10]. Of the 2156 participants who were over 55 years of age and had at least moderately severe symptomatic hip/knee OA, 57.3% died and 38.1% experienced cardiovascular events after a median of 13.2 years. Low function scores and walking disability were independently associated with an increased all-cause mortality [11].

The main objective of this study was to compare the mortality pattern of TKA patients with that of the general population. Data on preoperative comorbidity, socioeconomic status or life habits of our patients were not available. Bias caused by selection of the patients and postoperative medical interventions may have covered the influence of the prosthesis itself on the mortality.

The mortality pattern of TKA patients deviates from that of the normal population: it is reduced during the first 10 postoperative years, but starts a linear increase soon after surgery reaching that of the general population at that time. The reasons for the late mortality excess in our cohort are not known. Alzheimer's disease and dementia, and genitourinary diseases were associated with increased mortality after 20 years. In theory, TKA induced wear particles in circulation might expose to systemic neurological diseases such as Alzheimer's disease and dementia. However, we are not aware of any potential pathological mechanism behind this. Among accidents complications, e.g., periprosthetic fractures and septic prosthetic joint infections may have had small influence on this phenomenon. After the 20th postoperative year, the SMR for accidental mortality was 1.94, but the number of deaths was only 19. In future TKA patients will be younger than today. During 10 years extending from 1998 to 2007 the number of TKA patients under 55 years of age in Sweden increased five-fold and TKA is now the preferred treatment method for young OA patients [29]. In Finland, the annual cumulative incidence of TKAs in the age group of 30 to 59 years has increased 130-fold from 1980 to 2006 among patients operated on for OA [30]. Thus, much longer follow-up times are to be expected and the comorbidity of these patients and their increased long-term mortality must be taken into account.

Conflict of interest statement

All authors declare that they do not have any conflict of interest relating to the paper.

Ethical statement

This study was approved by the National Institute for Health and Welfare, decision THL/1615/5.05.00/2013. The study subjects were not

contacted and therefore no informed consents were required according to the Finnish regulations.

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