Increased long-term risk for hypertension in kidney donors – a retrospective cohort study

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SUMMARY

Kidney donors may be at increased risk of end-stage renal disease and premature mortality. Elevated blood pressure after donation may contribute to the increased risks. In this cohort study, we have assessed long-term risk for the development of hypertension in kidney donors compared to a control group potentially eligible as donors. Follow-up data were obtained from previous living kidney donors. A healthy control group with baseline assessment from similar time periods as the donor nephrectomies was selected. Hypertension was defined as blood pressure >140/90, use of blood pressure medication, or established diagnosis of hypertension. Stratified logistic regression was used to estimate risk of hypertension at follow-up, adjusted for systolic blood pressure at baseline, age at follow-up, time since donation/baseline, gender, smoking at baseline, and BMI at baseline. A total of 368 donors (36%) had hypertension at follow-up, and 241 of these (23%) were using blood pressure medication. In adjusted stratified logistic regression analyses, odds ratio for hypertension was significantly increased (1.25, 95% confidence interval 1.12–1.39, $P < 0.001$) in donors compared with controls. Kidney donors appear to be at increased long-term risk for hypertension compared with healthy controls. This finding supports regular follow-up of blood pressure in kidney donors.

Introduction

Living kidney donors derive no medical benefit from donation. In a previous publication from this donor cohort, we showed that both all-cause mortality and cardiovascular mortality were increased among donors compared to healthy controls [1]. Elevated blood pressure is a potential consequence of donor nephrectomy, and in the general population, hypertension is associated with long-term risk of end-stage renal disease [2], cardiovascular disease [3], and premature death [4].

Previous publications examining the development of hypertension after kidney donation have reported inconsistent data [5 – 9]. The long-term risk of living donation has been accepted as sufficiently low to justify the practice, but most studies done in the past addressing blood pressure after donation have been limited by short follow-up, small sample sizes, or inadequate control group [10 – 16]. However, later studies with longer

follow-up and more appropriate control groups have demonstrated an increased risk of hypertension in previous kidney donors [17,18].

We conducted a retrospective cohort study among a large sample of kidney donors to investigate the long-term risk for the development of hypertension after donation. For comparison, we selected control persons that had been medically screened in a large health survey performed in approximately similar time periods as the donor nephrectomies, selecting controls who were healthy at that time.

Materials and methods

In Norway, all kidney transplants and also all living donor nephrectomies are performed at Oslo University Hospital, Rikshospitalet. The predonation workup and postdonation controls of kidney donors are performed at their local hospitals. Before a final acceptance, the medical workup of each potential living donor is evaluated at Oslo University Hospital by a multidisciplinary medical team consisting of nephrologists, radiologists, immunologists, and transplant surgeons. Postdonation all donors are offered lifelong medical follow-up free of charge, and health information is reported to the Norwegian Living Donor Registry.

This cohort consists of living kidney donors who donated between 1972 and 2007 at Oslo University Hospital. From the hospital records, baseline data on 1422 donors were available. Through time, medical criteria for acceptance of a living donor have varied. For this analysis, only donors fulfilling standard donation criteria were included. Donors who did not fulfill these donation criteria at baseline were excluded from the study, and the exclusion criteria at time of donation were as follows: office systolic blood pressure above 140 mmHg, diastolic blood pressure above 90, body mass index above 30.0 kg/m^2, below 17 kg/m^2, or fasting glucose over 7 mmol/l. We also excluded donors over 70 years of age at time of donation, donors using blood pressure medication and those with estimated glomerular filtration rate under 70 ml/min/1.73 m^2. In addition, those with different comorbidities detected during predonation workup were excluded rendering a final study cohort of 1029 donors. To ensure that the comparison would be appropriate, the same exclusion procedure was applied to the control group. A flow chart for excluded and included study participants is shown in Fig. 1. We retrieved donor follow-up data from the time period between 2008 and 2013. Donors were evaluated at thirty-three different hospitals, and the results of the evaluation were submitted to the Living Donor Registry.

Control groups were included from the HUNT population surveys – a large longitudinal population health study from the county of Nord-Trøndelag. This county

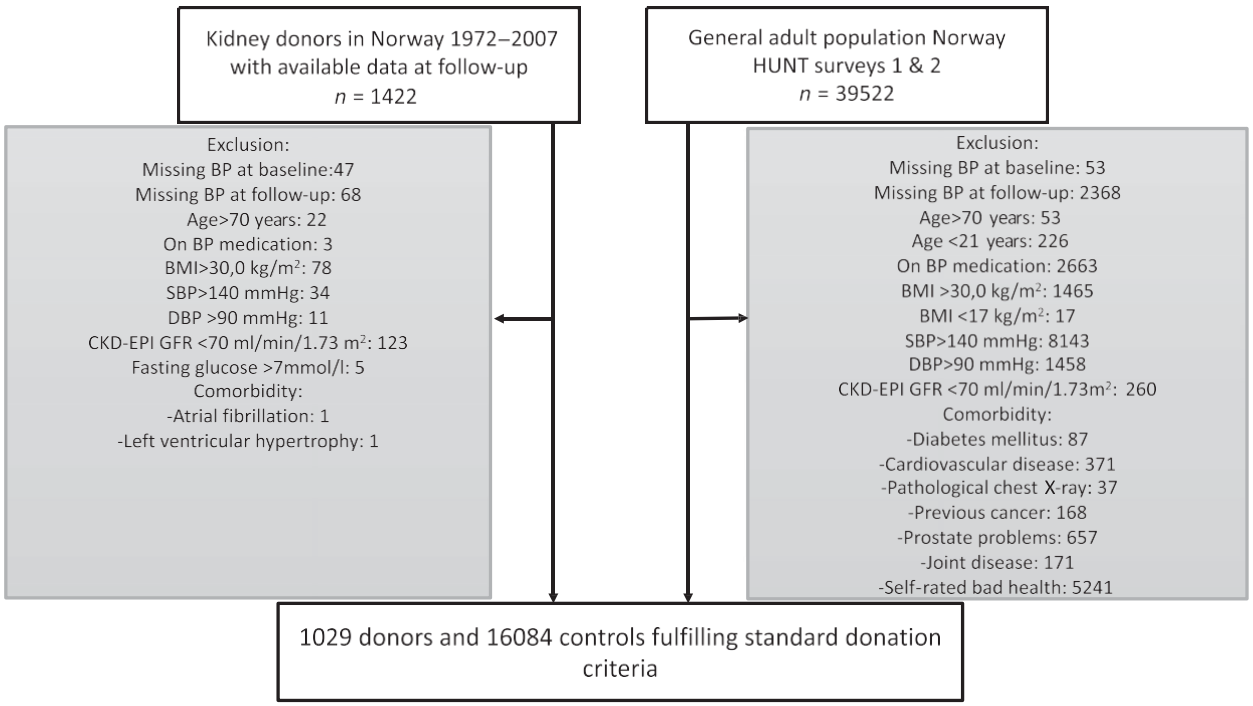

Figure 1 Baseline selection criteria.

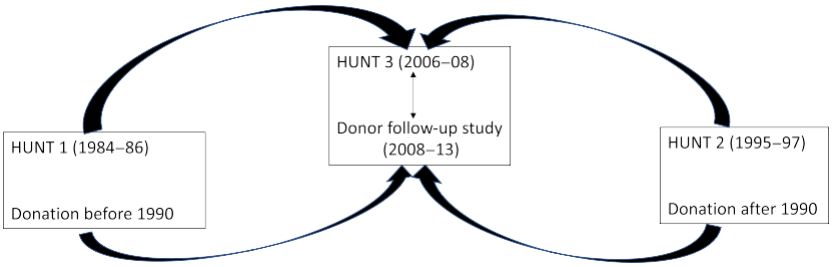

Figure 2 Stratification model.

is located in the middle part of Norway and has a demographical and occupational structure closely representative of the whole of Norway; however, there are no large cities represented. The educational level, average income, and prevalence of current smokers are slightly lower than the average for the whole country. Regarding sources of income, industry, morbidity, and mortality, the region is relatively representative of Norway. A closer description of the survey can be found at the HUNT study homesite (www.ntnu.edu/hunt). HUNT1, HUNT2, and HUNT3 surveys have been completed at 11-year intervals; 1984–1986 (HUNT1), 1995–1997 (HUNT2), and 2006–2008 (HUNT3). The HUNT1, HUNT2, and HUNT3 surveys registered data on comorbidities, blood pressure and body mass index at all three time points. In addition, HUNT2 and HUNT3 also included blood tests.

The HUNT3 study was performed during the same time period as the donor follow-up data were collected. The outcome of both groups was compared at this time.

For the statistical analysis, it was important to include controls who were healthy at a time as close to the donor ‘s nephrectomy as possible. Consequently, donors were divided into two groups reflecting the time periods that the HUNT1 and HUNT2 surveys were conducted (Fig. 2). The first group consists of donors who donated before 1990. This time period corresponds to the time of the HUNT1 survey. The second group consists of donors who donated after 1990. This time period corresponds to the time of the HUNT2 survey.

Outcomes of donors from the first group (donation before 1990) were compared to appropriate HUNT3 controls who also participated in the HUNT1 study. The HUNT1 study was performed in a similar time period as these donors donated, and all the controls who fulfilled donation criteria were selected for the analysis.

Outcomes of donors from the second group (donation after 1990) were compared to appropriate HUNT3 controls who also participated in the HUNT2 study. The HUNT2 study was performed in a similar time period as these donors donated. The controls were also selected to be equally healthy as the donors were at the time of donation, based on available baseline data. However, for those HUNT3 controls that had their baseline data from the HUNT1 survey, blood tests were not available.

Since donors and controls did not have their baseline evaluations at exactly the same time, we adjusted for time since donation/evaluation. We also considered the possibility of an interaction between time period (donation before and after 1990) and donation for the outcome of hypertension.

During the donor workup, blood pressure was recorded manually and registered in the patient charts. The standard pretransplant workup of living donors requires two office blood pressure measurements <140/90 mmHg. The blood pressure value recorded for the donor in the study was chosen among the blood pressure written down in the donor ‘s chart as part of the pretransplant workup or the blood pressure measured the day before surgery. If several blood pressure measurements were available at baseline, the lowest recorded blood pressure was used. During follow-up, blood pressure evaluation was performed manually by a physician in an outpatient setting. The physician was instructed to measure blood pressure three times and record the mean of the last two readings. The physician also registered if the donor had been given the diagnosis of hypertension since donation, and/or was using blood pressure medication at the time of follow-up.

In HUNT1, office blood pressure was measured with a mercury sphygmomanometer two times with the control person in the sitting position. The mean of these two readings was used.

In HUNT2 and HUNT3, office blood pressure was also measured in a sitting position. Three consecutive Dinamap automatic oscillometric blood pressure measurements were recorded on, and the mean of the second and third readings was calculated. Each HUNT survey participant indicated on a questionnaire if he/she had previously used blood pressure medication, or was

Table 1. Baseline characteristics of kidney donors and controls.

Variables	Kidney donors		Controls	
	n	Means (SD) Frequencies (%)	*n*	Means (SD) Frequencies (%)
eGFR CKD-EPI	1027	92 (13.5)	8703	108.8 (13.4)*
Systolic BP, mmHg	1029	122.3 (9.8)	16 084	121.9 (10.2)
Diastolic BP, mmHg	1029	76.8 (7.3)	16 084	74.8 (8)
Age, years	1029	44.8 (10.8)	16 084	37.1 (10.1)
BMI, kg/m^2	971	24.5 (2.8)	16 055	23.9 (2.6)
Current smoking	862	345 (33.5)	14 864	4498 (28)
Male gender	1029	453 (44)	16 084	6323 (39.3)

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.

*HUNT 2 participants.

using blood pressure medication at the time of the survey.

The primary outcome chosen for the present study was hypertension, defined as any blood pressure above 140 mmHg systolic and/or above 90 mmHg diastolic, use of blood pressure medication, or a clinical diagnosis of hypertension reported to the survey or registry.

The IBM Statistical Package for the Social Sciences version 23 was used for the statistical analyses. The main analysis was performed using stratified logistic regression with hypertension as an outcome and adjusting for age at follow-up, systolic blood pressure at baseline, time since donation (participation in HUNT1 or HUNT2 survey for controls), gender, smoking at baseline, and BMI at baseline. Because of missing baseline data for smoking (16.2 %) and BMI (5.6 %) among donors, analyses were repeated using multiple imputation. The stratified logistic regression analysis was repeated after adding change in body mass index from baseline to follow-up, to see if this would further affect the association between kidney donation and hypertension at follow-up. A sensitivity analysis was performed for the outcome of treated hypertension.

Blood pressure difference from baseline to follow-up measurements was calculated and then divided by the number of years between baseline and follow-up to estimate a yearly blood pressure increase. To compare the groups, a regression analysis was made for variables predicting increase in systolic blood pressure per year in participants without blood pressure medication at follow-up. We did not include those that used blood pressure medication at follow-up, since this may bias the analysis. This secondary analysis was performed using multiple linear regression. Possible associations between blood pressure increase and eGFR <60 ml/min at the time of follow-up were assessed using independent sample *t*-test.

A subset of donors and controls had available data on urine albumin–creatinine ratio. We calculated urine albumin–creatinine ratio in donors and controls with and without hypertension.

The Regional Committees for Medical and Health Research Ethics (REC) approved this study prior to data collection (approval ID: 2009/1588).

Results

Data from 1029 donors that fulfilled the standard donation criteria were included. Mean age at donation was 44.8 years (Table 1) and 56.1 years at time of follow-up. Mean observation time was 11.3 years since donation. Three-hundred and sixty-eight (35.8%) donors had hypertension at time of follow-up, and 241 (23.4%) were using one or several antihypertensive drugs.

A total of 16 084 controls who had available follow-up data in HUNT3, and also in the HUNT1 or HUNT2 survey, were included. Mean age at baseline survey was 37.1 years in the control group and 53.5 years at time of follow-up. Mean time since previous survey was 16.4 years. Among the controls at total of 4316 (26.8%) persons had developed hypertension and 1742 (10.8%) used antihypertensive drugs at the time of follow-up (Table 2).

Table 3 shows the odds ratio for hypertension in kidney donors compared with controls. The unadjusted risk for the outcome of hypertension associated with

Table 2. Characteristics at time of follow-up.

Variables	Kidney donors		Controls	
	n	Means (SD) Frequencies (%)	*n*	Means (SD) Frequencies (%)
Time since donation, years	1029	11.3 (8.1)	16 084	16.4 (5.7)*
eGFR CKD-EPI	1029	71 (14.5)	15 974	97.9 (14.2)
eGFR <60 ml/min	1029	216 (21)	15 974	236 (1.5)
Systolic BP, mmHg	1029	130 (17.2)	16 084	127.1 (16.4)
Diastolic BP, mmHg	1026	79.6 (9.4)	16 082	72.8 (10.4)
Age, years	1029	56.1 (12.4)	16 084	53.5 (11.1)
BP medication user	1029	241 (23.4)	16 084	1742 (10.8)
Hypertension	1029	368 (35.8)	16 084	4316 (26.8)
Urine albumin–creatinine ratio, mg/mmol	517	5.2 (22.2)	1365	2.8 (4.2)

BP, blood pressure; eGFR, estimated glomerular filtration rate.

*Time since last examination.

Table 3. Odds ratio for hypertension in kidney donors versus controls.

	Unadjusted	Adjusted 1*	Adjusted 2†
Time since donation	1.06 (1.04–1.08, $P < 0.001$)	1.04 (1.02–1.06, $P < 0.001$)	1.05 (1.04–1.05, $P < 0.001$)
Male gender	1.14 (1.08–1.21, $P < 0.001$)	0.85 (0.80–0.91, $P < 0.001$)	0.86 (0.81–0.91, $P < 0.001$)
Smoking status	1.03 (0.97–1.10, $P = 0.31$)	1.13 (1.06–1.21, $P < 0.001$)	1.13 (1.06–1.20, $P < 0.001$)
BMI	1.11 (1.10–1.13, $P < 0.001$)	1.06 (1.05–1.08, $P < 0.001$)	1.06 (1.05–1.07, $P < 0.001$)
Age	1.04 (1.04–1.05, $P < 0.001$)	1.03 (1.03–1.04, $P < 0.001$)	1.03 (1.03–1.04, $P < 0.001$)
Systolic blood pressure	1.05 (1.04–1.05, $P < 0.001$)	1.04 (1.04–1.04, $P < 0.001$)	1.04 (1.04–1.04, $P < 0.001$)
Kidney donation	1.63 (1.46–1.81, $P < 0.001$)	1.35 (1.19–1.53, $P < 0.001$)	1.25 (1.12–1.39, $P < 0.001$)

BMI, body mass index.

*Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow-up, and systolic blood pressure at baseline.

†After multiple imputation.

Table 4. Summary of regression analyses for variables predicting yearly increase in SBP in participants without blood pressure medication at follow-up.

Variables	*B*	95 % CI for *B*	*P* value
Male gender	0.04	-0.01, 0.08	0.096
Smoking status	0.02	-0.02, 0.06	0.38
Baseline SBP	-0.03	-0.04, -0.03	<0.001
Baseline BMI	0.04	0.03, 0.04	<0.001
Age at follow-up	0.03	0.03, 0.03	<0.001
Kidney donation	0.29	0.20, 0.38	<0.001

B, unstandardized coefficient; BMI, body mass index; SBP, systolic blood pressure.

The blood pressure difference from baseline to follow-up measurements was calculated and divided by number of years between the two time points to estimate a yearly blood pressure increase.

kidney donation was 1.63 (95% confidence interval (CI) 1.46–1.81, $P < 0.001$). In the analysis adjusted for covariates, odds ratio was 1.35 (CI 1.19–1.53, $P < 0.001$). In the main analysis after multiple imputation, odds ratio for hypertension was 1.25 (CI 1.12–1.39, $P < 0.001$). For the outcome of treated hypertension, there were similar results.

Among participants without blood pressure medication at follow-up, kidney donation was associated with a larger yearly systolic blood pressure increase than in controls ($P < 0.001$), (Table 4).

We did not find any association between blood pressure increase and eGFR <60 ml/min at the time of follow-up in the donors.

Adjusting the main analysis for an increase in body mass index from baseline to follow-up did not affect odds ratio for hypertension after kidney donation.

We did not find a difference in the association between kidney donation and hypertension according to the two time periods (donation before and after 1990).

At the time of follow-up, mean urine albumin–creatinine ratio in controls without hypertension was 2.4 mg/mmol (SD (standard deviation) 3.8) and 3.5 mg/mmol (SD 4.9) in controls with hypertension. In donors without hypertension, mean urine albumin–creatinine ratio was 2.6 mg/mmol (SD 9.1) and 10.2 mg/mmol (SD 35.3) in donors with hypertension.

Discussion

In this study, we have shown that standard criteria for kidney donors had a higher long-term risk for the development of hypertension compared to healthy selected controls. Kidney donors also had a significantly larger yearly systolic blood pressure increase compared to nondonor controls. Albuminuria appears to be associated with hypertension in donors. This finding, however, remains inconclusive due to large proportion of missing data.

Knowing the long-term risk for the development of hypertension associated with kidney donation is important to potential donors and their healthcare providers. Previous controlled studies on kidney donor blood pressure show varying results [5 – 10,12,13,17,19 – 23]. Most studies are retrospective, and some are limited by the quality of the control groups [11,12,14 – 16,21].

Our finding that donors have increased risk of hypertension when compared with suitable controls reaffirms what is found in two previous studies [17,18]. One retrospective study on African American live donors from the United States used techniques of restriction and matching to select healthy nondonor controls. Risk of hypertension was about twofold for donors compared to controls an average of 6 years after donation [17].

Most recently, Holscher *et al.* [18] retrospectively matched controls with donors through a propensity score model. They found a 19 % increased risk of hypertension in donors median 6 years after donation compared with a weighted cohort of healthy controls.

The authors constructed a cohort of nondonor controls from two prospective cohort studies. Follow-up information on incident hypertension in both donors and controls was self-reported on study visits and not from actual blood pressure measurements.

Selecting an adequate control group is important when analyzing kidney donor outcomes [24]. Ideally, the controls should be healthy enough to donate themselves. Even if they are not evaluated for donation, they should have performed a clinical and biochemical evaluation similar to what donors do during workup. For an optimal comparison, controls should have their baseline evaluation in the same time period as donor nephrectomies. Within the design of this study, we have attempted to address these prerequisites. We retrospectively selected controls who fulfilled standard donation criteria in a similar time period as the donors donated. With this design, we increase the probability that the control population would hypothetically have met donor criteria at the time of donation. However, there might still be differences between donors and medically screened and fit healthy nondonors. Therefore, a control group of potential donors that were not used due to lack of compatibility or being one of several potential donors might be the most appropriate controls. Such data on declined donors are not available, and a properly sized study using this approach is most likely not feasible.

Using a different approach to selecting controls, Najarian *et al.* [6] included sixty-five siblings and sixty-three donors. After mean follow-up interval of 23.7 years after nephrectomy, there were no significant differences in hypertension between the groups. This is an important study, but is likely to have been underpowered due to small sample size, increasing the likelihood of false-negative findings.

Only few prospective studies addressing blood pressure after donation have previously been published. In one of these studies, Kasiske *et al.* followed 182 donors with 173 matched healthy nondonors 36 months after donation. There was no statistically significant difference in blood pressure between the two groups at follow-up [10]. However, this study was limited by short observation time.

In a meta-analysis, Boudville *et al.* [25] concluded that within 5–10 years after donation blood pressure increases by an extra 5 mmHg in donors with reference to the expected increase associated with aging. The authors based their conclusion on five controlled primary studies [6,7,9,13,21]. In most of these studies, controls were included based on being healthy at the time of donor follow-up, and not at time of donation, which is when the donor is screened and found to be healthy enough for donation. Using controls who are healthy at the time of donor follow-up will skew results

in favor of controls and increase the likelihood of false-positive findings.

In another large retrospective study from Canada based on health administrative data, medical assessment of the controls was performed at the time of donation [22]. The authors also excluded controls that were previously hospitalized or had previous cardiovascular or renal disease. After a mean follow-up of 6.2 years, the rate of diagnosed hypertension was higher in donors compared to controls (16.3 % vs 11.9 %). Our long-term data are in line with this observation.

In a previous study, we found an increased all-cause and cardiovascular mortality among donors compared to healthy controls potentially eligible for donation [1] and the increased prevalence of hypertension at long-term follow-up may further explain the observed increase in cardiovascular mortality among Norwegian kidney donors.

One would expect that the development of hypertension could occur late after donation, since donors are relatively young and relatively healthy at the time of donation. This aspect has been addressed by Sanchez *et al*. [26]. They evaluated occurrence of hypertension and time after donation. In their cohort of donors, the median time to diagnosis of hypertension was 15.3 years after nephrectomy. These data further illustrate that long-term follow-up on blood pressure after donation is important.

The current study has several strengths and limitations. We included controls on similar terms as donors. However, controls did not undergo the same thorough medical screening procedures as the donors, and some health issues might remain undetected by our inclusion and exclusion criteria. We did not have blood tests in HUNT1 participants, so baseline kidney function is unknown for these controls. The exact time of the baseline assessments and the follow-up assessments were not similar between the two groups, and although we adjusted for time since baseline evaluation in both groups, we cannot exclude any bias due to slight differences regarding the time of assessment. Time to event analyses is more informative in donor outcome studies and could be regarded as the 'gold standard' for such observational studies. However, we did not have data available for this method.

It is not likely that blood pressure measurements were performed in a standardized manner for all participants, since the blood pressure recordings for the donors were obtained from medical records, and we had no way of instructing or assuring how measurements were done.

Donors might be more likely to pursue a healthy lifestyle after donation, which could also introduce bias. Access to health care differs between the two groups. Donors are offered lifelong follow-up free of charge. Given that the study population consisted of Caucasians only, our findings might not be valid for other ethnicities. Last, most donors are related to their recipients and genetic predispositions for hypertension could therefore be more frequent among donors than controls. In case of nonrelated donation where the donor is a life partner of the recipient, lifestyle factors can affect both transplantation in the recipient and risk of hypertension in the donor.

Notable strengths of this study include a high number of donors with available blood pressure readings at follow-up and a long observation time. We selected a control group potentially eligible for donation in a time period similar to the time of the donor 's nephrectomy. This way, we were able to compare the donor outcome with controls who had a comparable health status as the donors at the time of donation.

In conclusion, kidney donors may be at higher long-term risk for the development of hypertension after donation, compared to a healthy control group eligible to be donors. Donors should be informed of this risk and other potential risks of donation, before deciding whether to start kidney donor evaluation. These findings support lifelong follow-up of kidney donors.

Authorship

AJH: collected the data, participated in the statistical analyses, participated in planning of research design, and drafted paper. SH, NL, DOD, HP, KB, AR, KM, AH, and HH: participated in writing of the manuscript and approved final version of paper. GM: participated in the planning of research design, statistical analyses, writing of the manuscript, and approved final version of paper.

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Conflicts of interest

K.I. Birkeland has received honorariums to the university from the following in the past two years (consulting fees or paid advisory boards): MSD Europe, AstraZeneca, Boehringer Ingelheim, Novo Nordisk Pharma, Lilly, Sanofi-Aventis, Roche; received travel support from AstraZeneca, MSD; and received grant support from industry: AstraZeneca, Boehringer Ingelheim, MSD, Novo Nordisk Pharma, Lilly, Sanofi-Aventis, Roche. D.O. Dahle, S. Hallan, A. Reisæter, H. Holdaas, G. Mjøen, H. Pihlstrøm, A.J. Haugen, A. Hartmann, K. Midtvedt, and N.E. Langberg have no conflicts of interest to disclose.

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