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No association between frequent apheresis donation and risk of fractures: a retrospective cohort analysis from Sweden

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Abstract

Background—Citrate anticoagulation during apheresis induces transient alterations in calcium homeostasis. It is unknown if repeated, transient alterations in calcium homeostasis, experienced by repeated apheresis donors, affects bone turnover to increase fracture risk. Our aim was to investigate risk of osteoporotic and non-osteoporotic fracture among voluntary, frequent apheresis donors.

Study design and methods—All apheresis donors were identified from the Scandinavian donations and transfusions database (SCANDAT2) which includes information on over 1.6 million blood donors from Sweden and Denmark from 1968 and 1981, respectively. Only data from Sweden were used for these analyses. Information on fractures was obtained by linking SCANDAT2 to hospital registers. Poisson regression was used to compute incidence rate ratios of fractures in relation to cumulative number of apheresis donations, both overall and in fixed time-windows.

Results—We included a total of 140,289 (67,970 female and 72,319 male) apheresis donors were identified from the SCANDAT2 database and were followed for up to 23 years. We observed no association between apheresis donation frequency and fracture risk neither in the overall, nor in the fixed length time windows. The incidence rate ratio of fractures in donors with ≥100 cumulative apheresis donations was 0.99 (95% confidence interval, 0.92–1.06) compared to

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Disclosure Summary

The authors have nothing to disclose.

donors with 9–24 donations. Results were similar in analyses stratified by sex, and in analyses restricted to post-menopausal women.

Conclusions—Absence of association between repeated apheresis donation and fracture risk indicates that apheresis collection is safe with regards to bone health.

Keywords

Apheresis; fracture; osteoporosis; citrate; anticoagulation

Introduction

Apheresis involves the collection of specific blood components, such as platelets, plasma, or peripheral blood stem cells, individually or in combination, with the remnants returned to the donor or patient[1]. During apheresis, anticoagulation is necessary to prevent coagulation and clotting in the apheresis circuit. Here, citrate is the preferred because of its safety and effectiveness *viz-a-viz* the alternative heparin[2].

Acute metabolic effects of apheresis include hypocalcaemia, hypercalciuria, secondary hyperparathyroidism, hypomagnesemia, and metabolic alkalosis, all of which are attributed to ionized calcium-citrate complexes[3–6]. For example, Silberstein *et al* reported an 18% reduction in ionized calcium, a net calcium loss of 150 mg, and an acute 280% increase in parathyroid hormone (PTH) levels[3]. The acute serum PTH elevations in turn has been related to a reduction in 1,25-dihydroxyvitamin D and increase in the bone turn over marker osteocalcin[7,8].

These observations collectively call for speculations about the effect of apheresis on bone mineral health. Of note, a reduced lumbar spine bone mineral density (BMD) has been observed among apheresis donors in one study[9]. Recently, changes in the bone turnover in response to single citrate load at a dose similar to plateletpheresis have also been described[10,11]. However, in view of the long history of apheresis surprisingly little is known about risk of fractures among frequent apheresis donors[12].

We therefore took advantage of information on apheresis donations and occurrence of fractures in a large cohort of blood donors to assess the association between the two.

Methods

Data sources

Data on apheresis donations were extracted from the Scandinavian donation and transfusion (SCANDAT2) database, a bi-national database of blood donation and transfusion activities, described in detail elsewhere[13]. In summary, the database was created from computerized registers maintained by the Swedish and Danish blood banks since 1968 and 1981, respectively. Following data collection and cleaning, the database was linked with nationwide population and health data registers using unique national registration numbers available for all individuals in both countries[14,15]. The database thus provides long-term follow-up of a large number of donors for a range of health outcomes, including hospital

care, fractures and surgery. We have previously used this database to study the occurrence of a range of diseases in both blood donors and transfused patients[16–19]. Because apheresis collection of blood units has only been practiced sporadically in Danish blood banks, the present analyses were restricted to Swedish data only.

Outcome ascertainment

Occurrence of fractures was ascertained from the Swedish patient register, which records data on inpatient care in Sweden during the entire study period, and outpatient specialist health care from 2004[20]. Classification of fractures was based on the international classification of diseases (ICD) revisions 9 and 10 (See Supplementary Table 1, for specific codes). The main outcome of interest was 'all fractures', but we also specifically analyzed occurrence of 'osteoporosis-related fractures', which *a priori* was defined as fractures of the forearm, proximal humerus, proximal femur, and ankle. Tooth and patellar fractures were excluded from analysis.

Study design and statistical analyses

From the SCANDAT2 database we extracted all available data on Swedish blood donors who had performed at least one apheresis donation between 1990 and 2012, excluding autologous donations. Analyses were restricted to this relatively recent period to avoid results being influenced by suspected economic motivations for blood donation during earlier periods[16], as well as to avoid effects of possible underreporting of numbers of apheresis procedures during the 1980's.[13] We conducted a retrospective analysis following donors from the first recorded apheresis donation, in or after 1990, until death, emigration, or end of follow-up (December 31st, 2012), whichever occurred first. Within this follow-up interval donors were followed for the fracture outcome of interest (i.e. any fracture or osteoporotic fractures), In order to count only mutually unrelated events, upon occurrence of a fracture in a donor, he/she would re-enter follow-up only after a six month waiting period.

In the main analyses we assessed the effect of the total number of apheresis donations recorded during the study period, irrespective of type of apheresis procedure. The cumulative number of apheresis donations was considered time-dependently, so that subjects would move between categories with each successive donation. As citrate exposure may differ between plasmapheresis and plateletpheresis procedures, we also considered the number of plasma and platelet apheresis donations separately. Because we hypothesized that the putative effects of number of apheresis donations on the risk of fractures may have variable latency, we also assessed the number of donations performed in the most recent 2, 5, and 10 years. Again, this was done time-dependently by tracking the donation activity of all donors at every given time point during their follow-up. Relative risks of fractures, expressed as incidence rate ratios (IRR), in relation to number of apheresis donations were estimated using Poisson regression. Analyses were adjusted for age (in 1-year categories), sex, calendar period of observation (in 1-year categories), and time since most recent apheresis donation. Separate analyses were conducted for number of apheresis donations overall and for number of apheresis donations in the three fixed length exposure windows. Analyses were performed both for all donors combined and stratified by sex. We also performed analyses restricted to postmenopausal women (i.e., women aged ≥ 50 years)

because we hypothesized that this group might be more susceptible to negative effects of repeated perturbations in calcium homeostasis. All variables were treated as categorical. Trend tests were performed by fitting the variable for number of apheresis donations as a linear term. Ninety-five percent confidence intervals (95% CIs) were constructed using Wald tests.

All data processing and statistical analyses were performed using SAS Statistical analysis software (Version 9.4, SAS Institute, Inc., Cary, North Carolina). P-values < 0.05 were considered statistically significant.

Ethics

The creation of the SCANDAT2 database and the conduct of this study were approved by the regional ethics committees in Stockholm, Sweden in accordance with the national legislation.

Results

Following exclusion of donors with only whole blood, autologous, or failed donations, 140,289 apheresis donors were included in the analyses. Of these, 67,970 (48%) were women. The mean age at first apheresis donation among female and male donors was 31.5 and 33.2 years respectively. Most apheresis donations (3,100,849; 95.7%), were plasma donations, as presented in Table 1.

Relative risks of fractures overall, and of osteoporotic fractures specifically, in relation to cumulative number of apheresis donations are presented in Table 2. There was no evidence of an association between cumulative number of apheresis donations and risk of fractures neither when we considered fractures overall, nor when we specifically assessed osteoporosis-related fractures. Among donors in the most extreme exposure category, with ≥100 apheresis donations the relative risks of fractures were 0.99 (95% confidence interval [CI], 0.92–1.06) for both sexes combined, 1.00 (95% CI, 0.89–1.12) for women, 1.08 (95% CI, 0.94–1.24) for postmenopausal women, and 0.98 (95% CI, 0.90–1.07) for men, as compared with donors with 9–24 cumulative apheresis donations. Similar patterns emerged upon analyzing the group of donors with fewer apheresis donations and when we analyzed osteoporosis-related fractures separately (Table 2). We also detected no statistically significant trends when number of apheresis donations was fitted as linear terms (data not shown).

Table 3 presents relative risks of fractures, in relation to number of apheresis donations in the most recent 2, 5, and 10 year windows. Again, there was no association between number of apheresis donations and fracture risk in neither exposure window. For men and women combined, the IRR of fractures overall was 0.94 (95% CI, 0.85–1.03) among donors with ≥16 apheresis donations in the most recent 2 years, compared to donors with 4–7 donations in the same period. Patterns were similar in the 5- and 10-year windows, with IRRs of 0.97 (95% CI, 0.88–1.06) and 0.95 (95% CI, 0.87–1.04) among donors with ≥40 donations in the most recent 5 years, and ≥80 donations in the most recent 10 years, respectively. Effects did not vary in analyses stratified by sex, nor when restricted to postmenopausal women (Table

3). Again, trend tests revealed no conspicuous departure from the overall picture (data not shown).

Lastly, results did not vary when analyses were repeated considering the number of plasma and platelet apheresis donations separately among the 135,259 and 11,345 donors who ever donated plasma and platelets, respectively (data not shown).

Discussion

This is the first study to evaluate the long-term effects of frequent apheresis donation on fracture risk among healthy, voluntary donors. We find no association between frequent apheresis donation, during which donors have repeatedly been exposed to intravenous citrate anticoagulation, and risk of fractures. Although acute perturbations in calcium metabolism following apheresis donation have been reported previously[5,21,22], we provide evidence that such repeated acute effects among frequent apheresis donors do not cumulatively impact long-term fracture risk.

Our study has several merits. It is based on a very large and unrestricted selection of voluntary, healthy apheresis donors who were followed over a long time period. Further, the study design, the well-defined cohort of over 140,000 apheresis donors with a broad age range, up to 23 years of follow-up, and the use of complete medical registers for the ascertainment of fractures makes our results robust and the study adequately powered. However, we do acknowledge some potential weaknesses. Our investigation is an observational, register-based record-linkage study, where we were unable to obtain more detailed data about fracture diagnoses for validation. However, although this could result in both some degree of misclassification and under-reporting of fractures, we believe that outcome misclassification should be minimal. Also, since the extent of this misclassification is unlikely to be related to prior apheresis donation frequency, it should not impact the validity of our observation. Further, the use of fracture coding has been previously shown to be of high quality particularly for hip fractures, which are mostly osteoporotic and the specificity in the Swedish inpatient register is shown to be close to 100%[14,23]. We also acknowledge that in the current study the majority of the apheresis donations are plasma where the citrate exposure is lesser compared to other types of apheresis donations since much of the citrate introduced in the extracorporeal circuit is not returned to the donor[24]. Nevertheless, evidence suggests that PTH surges occur even with very little exogenous citrate supporting the interpretation of the present study[25]. Our study is limited by lack of data on other characteristics of interest such as serum calcium, PTH or BMD which precludes us from providing a comprehensive description of short- and long-term metabolic changes among apheresis donors, but this is not the primary objective of the study. Our database is also limited by a lack of information on additional potentially important covariates such as smoking, body mass index and other medication that could influence fracture risk, which could result in some degree of residual confounding that we cannot account for. It is thus possible that a deleterious association between apheresis donation and fracture risk was masked by a gradient of healthier behavior among the more frequent apheresis donors. Although we have no definitive data on these covariates, we do not believe this to be the case given the complete lack of an association that we observe, and the fact

that we have previously not observed any clear associations between donation frequency and health outcomes[26]. Along the same lines, since all fractures were ascertained through the Swedish patient register, which only records specialized outpatient care since 2004, fractures that would not necessitate surgery and/or hospital admissions would not be captured before that date. As such, we likely underestimated the occurrence of less complicated fractures. However, because the degree of such underreporting is very unlikely to differ between infrequent and frequent apheresis donors, it should only lead to a decreased power and not affect relative estimates. A further limitation of the register-based design is the absence of data on actual citrate exposure, which unfortunately prevents us from accurate quantification of the association between citrate load and fracture risk and also doesn't allow us to provide data on a safe upper limit of citrate exposure. That said, given that we saw no increased risks even among donors with an average of at least 8 apheresis donations per year over 10 years, with an upper confidence interval of 1.04, current practices appear safe.

The side-effects of citrate infusion during apheresis are predominantly mild, transient and most often self-limiting. Perioral or peripheral paraesthesia secondary to hypocalcaemia is the most commonly observed side-effect, which is frequently reported[10,11]. Severe effects such as involuntary carpopedal spasm and progression to tetany are rare, but reported in a very small proportion (0.89%) of apheresis donors[27]. The aforementioned side-effects are almost entirely related to the decreased ionized calcium levels associated with citrate anticoagulation leading to secondary hyperparathyroidism. Such short-term alterations in calcium and phosphate balance have been reported to also associate with lower vitamin D levels and much speculated to have long term consequences on bone turnover, thereby increasing fracture risk[28].

To date, evidence of long term effects of these metabolic perturbations on bone turnover and fracture risk is almost entirely lacking. Several underlying mechanisms have been proposed that could contribute to elevated fracture risk among repeated apheresis donors, including i) repeated alterations in calcium-phosphate balance, and ii) recurring protein loss particularly those that relate to bone homeostasis[8]. Our study demonstrates that long-term increased risks of fractures are unlikely in apheresis donors. Given that exposure to citrate during apheresis decidedly affects calcium homeostasis, at least transiently, several potential explanations for our observations of no long term effects should be considered. Citrate-induced acute short term elevations in PTH levels could exert an anabolic effect by increasing the number of osteoblasts, as proposed previously[4,7,29]. Although this could be a possible underlying mechanism, it requires further confirmation from large population studies. Some support for a possible anabolic effect of repeated PTH spikes triggered by apheresis donations comes from Boot *et al.*, who demonstrated in a pilot study of postmenopausal women, slightly higher BMD among repeated apheresis donors compared to whole blood donors[9] thus demonstrating that such transient spurts have beneficial effects on bone. It is also possible that the cumulative citrate exposure experienced by the donors in this study was simply insufficient to have a detectable effect on fracture risk, or that a slight risk increase was masked by a "healthy donor effect", i.e. whereby frequent donors had a healthier behavior[16,26,30]. We also acknowledge that our results may have been influenced by calcium intake, since calcium supplementation is occasionally recommended for apheresis donors. However, although we have no specific data about this practice, it seems

unlikely to have had a major effect given that calcium supplementation is then only recommended transiently.

In conclusion, using a large database of blood donations, we observe no association between apheresis donations and fracture risk, suggesting that the repeated acute metabolic alterations in calcium homeostasis among frequent donors do not influence the risk of fractures. Although our results indicate that it is unlikely that frequent apheresis donors have increased risks of fractures, it does not necessarily preclude prophylactic calcium supplementation and detailed evaluation for secondary hyperparathyroidism among these donors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMD	Bone mineral density
ICD	International classification of diseases
PTH	Parathormone
SCANDAT	Scandinavian donations and transfusions database

References

1. Okafor C, Ward DM, Mokrzycki MH, Weinstein R, Clark P, Balogun RA. Introduction and overview of therapeutic apheresis. J Clin Apher. 2010; 25:240–9. [PubMed: 20806281]
2. Lee G, Arepally GM. Anticoagulation techniques in apheresis: from heparin to citrate and beyond. J Clin Apher. 2012; 27:117–25. [PubMed: 22532037]
3. Silberstein LE, Naryshkin S, Haddad JJ, Strauss JF 3rd. Calcium homeostasis during therapeutic plasma exchange. Transfusion. 1986; 26:151–5. [PubMed: 3006298]
4. Winters JL. Complications of donor apheresis. J Clin Apher. 2006; 21:132–41. [PubMed: 15880355]
5. McLeod BC, Price TH, Owen H, Ciavarella D, Sniecinski I, Randels MJ, Smith JW. Frequency of immediate adverse effects associated with apheresis donation. Transfusion. 1998; 38:938–43. [PubMed: 9767744]
6. Toffaletti J, Nissenson R, Endres D, McGarry E, Mogollon G. Influence of continuous infusion of citrate on responses of immunoreactive parathyroid hormone, calcium and magnesium components, and other electrolytes in normal adults during plateletapheresis. J Clin Endocrinol Metab. 1985; 60(5):874–9. [PubMed: 3980672]

7. Chen Y, Bieglmayer C, Hocker P, Dettke M. Effect of acute citrate load on markers of bone metabolism in healthy volunteers. Vox Sang. 2009; 97:324–9. [PubMed: 19508702]
8. Amrein K, Katschnig C, Sipurzynski S, Stojakovic T, Lanzer G, Stach E, Pieber TR, Dobnig H. Apheresis affects bone and mineral metabolism. Bone. 2010; 46:789–95. [PubMed: 19922822]
9. Boot CL, Luken JS, van den Burg PJ, de Kort WL, Koopman MM, Vrielink H, van Schoor NM, den Heijer M, Lips P. Bone density in apheresis donors and whole blood donors. Vox Sang. 2015
10. Bolan CD, Greer SE, Cecco SA, Oblitas JM, Rehak NN, Leitman SF. Comprehensive analysis of citrate effects during plateletpheresis in normal donors. Transfusion. 2001; 41:1165–71. [PubMed: 11552076]
11. Dettke M, Buchta C, Bieglmayer C, Kainberger F, Macher M, Hocker P. Short and long term effects of citrate on bonemetabolism and bone mineral density in healthy plateletph-eresis donors. J Clin Apheresis. 2003; 18:87.
12. Bialkowski W, Bruhn R, Edgren G, Papanek P. Citrate anticoagulation: Are blood donors donating bone? J Clin Apher. 2015
13. Edgren G, Rostgaard K, Vasan SK, Wikman A, Norda R, Pedersen OB, Erikstrup C, Nielsen KR, Titlestad K, Ullum H, Melbye M, Nyren O, Hjalgrim H. The new Scandinavian Donations and Transfusions database (SCANDAT2): a blood safety resource with added versatility. Transfusion. 2015; 55:1600–6. [PubMed: 25573303]
14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009; 24:659–67. [PubMed: 19504049]
15. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014; 29:541–9. [PubMed: 24965263]
16. Edgren G, Reilly M, Hjalgrim H, Tran TN, Rostgaard K, Adami J, Titlestad K, Shanwell A, Melbye M, Nyren O. Donation frequency, iron loss, and risk of cancer among blood donors. J Natl Cancer Inst. 2008; 100:572–9. [PubMed: 18398098]
17. Vasan SK, Rostgaard K, Ullum H, Melbye M, Hjalgrim H, Edgren G. ABO Blood Group and Dementia Risk--A Scandinavian Record-Linkage Study. PLoS One. 2015; 10:e0129115. [PubMed: 26042891]
18. Edgren G, Tran TN, Hjalgrim H, Rostgaard K, Shanwell A, Titlestad K, Wikman A, Norda R, Jersild C, Wideroff L, Gridley G, Adami J, Melbye M, Nyren O, Reilly M. Improving health profile of blood donors as a consequence of transfusion safety efforts. Transfusion. 2007; 47:2017–24. [PubMed: 17958530]
19. Sartipy U, Holzmann MJ, Hjalgrim H, Edgren G. Red Blood Cell Concentrate Storage and Survival After Cardiac Surgery. JAMA. 2015; 314:1641–3. [PubMed: 26501540]
20. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011; 11:450. [PubMed: 21658213]
21. Amrein K, Valentin A, Lanzer G, Drexler C. Adverse events and safety issues in blood donation--a comprehensive review. Blood Rev. 2012; 26:33–42. [PubMed: 21996651]
22. Makar YF, Butler MO, Cockersole GM, Gabra G, Serevitch JM. National audit of citrate toxicity in plateletpheresis donors. Transfus Med. 2002; 12:187–91. [PubMed: 12071875]
23. Ludvigsson JF, Michaelsson K, Ekbom A, Montgomery SM. Coeliac disease and the risk of fractures - a general population-based cohort study. Aliment Pharmacol Ther. 2007; 25:273–85. [PubMed: 17269989]
24. Evers J, Taborski U. Distribution of citrate and citrate infusion rate during donor plasmaphereses. J Clin Apher. 2016; 31:59–62. [PubMed: 26011445]
25. Haden ST, Brown EM, Hurwitz S, Scott J, El-Hajj Fuleihan G. The effects of age and gender on parathyroid hormone dynamics. Clin Endocrinol (Oxf). 2000; 52:329–38. [PubMed: 10718831]
26. Ullum H, Rostgaard K, Kamper-Jorgensen M, Reilly M, Melbye M, Nyren O, Norda R, Edgren G, Hjalgrim H. Blood donation and blood donor mortality after adjustment for a healthy donor effect. Transfusion. 2015

27. Mauricio R, de Sousa G, Seghatchian J. What's happening: an overview of potential adverse reactions associated with apheresis technology. Transfus Apher Sci. 2005; 33:351–6. [PubMed: 16226918]

28. Hiemstra TF, Casian A, Boraks P, Jayne DR, Schoenmakers I. Plasma exchange induces vitamin D deficiency. QJM. 2014; 107:123–30. [PubMed: 24131546]

29. Jilka RL, O'Brien CA, Ali AA, Roberson PK, Weinstein RS, Manolagas SC. Intermittent PTH stimulates periosteal bone formation by actions on post-mitotic preosteoblasts. Bone. 2009; 44:275–86. [PubMed: 19010455]

30. Atsma F, de Vegt F. The healthy donor effect: a matter of selection bias and confounding. Transfusion. 2011; 51:1883–5. [PubMed: 21790637]

Table 1

Characteristics of study population.*

	Women		Men	
	N=67,970	**(48.0%)**	**N=72,319**	**(52.0%)**
Age at first apheresis donation, N (%)				
<25 years	27 237	(40.1)	24 134	(33.4)
25–29 years	12 111	(17.8)	13 233	(18.3)
30–39 years	14 927	(22.0)	18 311	(25.3)
≥40 years	13 695	(20.1)	16 641	(23.0)
Mean age, years (SD)	31.5	(10.9)	33.2	(11.2)
Median duration of follow-up, years (IQR)	17.9	(13.8–23.0)	18.8	(13.9–23.0)
Cumulative number of apheresis donations, N (%)				
Plasma	1 258 763	(98.1)	1 842 086	(94.1)
Platelets	24 225	(1.9)	115 039	(5.9)
Blood group, N (%)				
A	30 195	(44.4)	32 417	(44.8)
AB	4 475	(6.6)	4 851	(6.7)
B	8 398	(12.4)	8 736	(12.1)
O	24 783	(36.5)	26 157	(36.2)
Unknown	119	(0.2)	158	(0.2)

*SD denotes standard deviation. IQR denotes interquartile range.

Table 2

Relative risks of fractures among apheresis donors in relation to cumulative number of apheresis donations.

	Number of apheresis donations									
	1 – 8		9–24		25 – 49		50 – 99		≥ 100	
All fractures	*Events; incidence rate ratios (95% confidence interval)*									
Both sexes	9 389	1.02 (0.99–1.06)	4 795	1.00 (ref)	2 731	1.00 (0.95–1.04)	1 810	0.97 (0.92–1.02)	1 041	0.99 (0.92–1.06)
Women	4 342	1.04 (0.99–1.09)	2 158	1.00 (ref)	1 180	1.00 (0.93–1.08)	720	0.96 (0.88–1.05)	358	1.00 (0.89–1.12)
Women age 50 years or above	1 762	1.08 (0.99–1.17)	906	1.00 (ref)	616	1.00 (0.91–1.11)	462	0.99 (0.89–1.11)	297	1.08 (0.94–1.24)
Men	5 047	1.01 (0.96–1.06)	2 637	1.00 (ref)	1 551	0.99 (0.93–1.05)	1 090	0.97 (0.90–1.04)	683	0.98 (0.90–1.07)
Osteoporosis related fractures										
Both sexes	3 814	1.06 (1.00–1.12)	1 903	1.00 (ref)	1 137	1.01 (0.94–1.09)	804	1.03 (0.94–1.12)	852	1.04 (0.96–1.13)
Women	2 246	1.07 (0.99–1.15)	1 103	1.00 (ref)	653	1.04 (0.94–1.14)	420	1.01 (0.90–1.13)	354	1.00 (0.88–1.13)
Women age 50 years or above	1 096	1.08 (0.97–1.19)	564	1.00 (ref)	412	1.07 (0.95–1.22)	307	1.05 (0.92–1.21)	203	0.99 (0.84–1.16)
Men	1 568	1.05 (0.97–1.15)	800	1.00 (ref)	484	0.98 (0.87–1.10)	384	1.05 (0.93–1.18)	498	1.07 (0.95–1.20)

Table 3

Relative risks of fractures among apheresis donors in relation to number of apheresis donations in the most recent 2, 5 and 10 years.

	Number of apheresis donations							
2-year exposure window	**1–3**		**4–7**		**8–15**		**≥16**	
All fractures	*Events; incidence rate ratios (95% confidence interval)*							
Both sexes	1 637	1.00 (0.92–1.08)	1 038	1.00 (ref)	991	0.95 (0.87–1.04)	924	0.94 (0.85–1.03)
Women	611	1.00 (0.88–1.14)	387	1.00 (ref)	377	0.98 (0.85–1.14)	311	0.89 (0.76–1.05)
Women age 50 years or above	158	0.95 (0.75–1.21)	121	1.00 (ref)	128	0.88 (0.69–1.14)	174	1.01 (0.78–1.30)
Men	1 026	0.99 (0.90–1.10)	651	1.00 (ref)	614	0.93 (0.84–1.04)	613	0.96 (0.85–1.09)
Osteoporosis related fractures								
Both sexes	576	1.05 (0.92–1.20)	358	1.00 (ref)	372	1.00 (0.86–1.15)	370	0.98 (0.84–1.15)
Women	290	1.08 (0.90–1.31)	175	1.00 (ref)	187	1.04 (0.84–1.28)	172	0.98 (0.78–1.23)
Women age 50 years or above	100	1.04 (0.76–1.41)	70	1.00 (ref)	79	0.94 (0.68–1.31)	108	1.06 (0.76–1.47)
Men	286	1.02 (0.84–1.23)	183	1.00 (ref)	185	0.96 (0.78–1.18)	198	0.98 (0.79–1.23)
5-year exposure window	**1–9**		**10–19**		**20–39**		**≥40**	
All fractures	*Events; incidence rate ratios (95% confidence interval)*							
Both sexes	4 287	1.05 (0.99–1.12)	1 419	1.00 (ref)	1 232	1.05 (0.97–1.13)	787	0.97 (0.88–1.06)
Women	1 706	1.09 (0.99–1.21)	538	1.00 (ref)	467	1.08 (0.95–1.23)	272	0.97 (0.83–1.13)
Women age 50 years or above	517	1.15 (0.97–1.36)	190	1.00 (ref)	193	1.00 (0.81–1.22)	179	1.10 (0.88–1.37)
Men	2 581	1.03 (0.95–1.11)	881	1.00 (ref)	765	1.03 (0.93–1.13)	515	0.97 (0.86–1.08)
Osteoporosis related fractures								
Both sexes	1 542	1.07 (0.97–1.19)	519	1.00 (ref)	485	1.08 (0.96–1.23)	341	1.05 (0.91–1.22)
Women	808	1.05 (0.92–1.21)	276	1.00 (ref)	243	1.04 (0.87–1.24)	162	1.01 (0.82–1.24)
Women age 50 years or above	321	1.09 (0.88–1.34)	124	1.00 (ref)	123	0.98 (0.76–1.26)	116	1.11 (0.85–1.45)
Men	734	1.10 (0.95–1.28)	243	1.00 (ref)	242	1.13 (0.94–1.35)	179	1.10 (0.89–1.34)
10-year exposure window	**1–19**		**20–39**		**40–79**		**≥80**	
All fractures	*Events; incidence rate ratios (95% confidence interval)*							
Both sexes	8 809	0.99 (0.94–1.04)	2 021	1.00 (ref)	1 321	0.94 (0.88–1.01)	654	0.95 (0.87–1.04)
Women	3 691	0.97 (0.90–1.05)	829	1.00 (ref)	508	0.92 (0.82–1.03)	221	0.92 (0.79–1.08)
Women age 50 years or above	1 280	1.04 (0.92–1.16)	368	1.00 (ref)	291	0.98 (0.84–1.14)	168	1.05 (0.87–1.27)

Men	5 118	1.01 (0.94–1.07)	1 192	1.00 (ref)	813	0.96 (0.88–1.05)	433	0.96 (0.86–1.08)	
Osteoporosis related fractures									
Both sexes	3 378	1.04 (0.96–1.12)	779	1.00 (ref)	579	1.04 (0.93–1.16)	300	1.07 (0.94–1.23)	
Women	1 855	1.02 (0.92–1.14)	425	1.00 (ref)	307	1.03 (0.89–1.20)	133	0.99 (0.81–1.21)	
Women age 50 years or above	819	1.04 (0.90–1.21)	233	1.00 (ref)	200	1.07 (0.88–1.29)	111	1.12 (0.88–1.41)	
Men	1 523	1.06 (0.94–1.19)	354	1.00 (ref)	272	1.04 (0.89–1.22)	167	1.16 (0.96–1.41)	