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Familial colorectal cancer risk may be lower than previously thought: A Danish cohort study

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ABSTRACT

Background: The risk of colorectal cancer (CRC) is reportedly increased two-fold if at least one first-degree relative (FDR) is affected with CRC, increasing to three- to four-fold if multiple FDRs are affected or if one FDR was diagnosed at a young age. We evaluated familial risk of CRC, systematically excluding monogenetic high-risk families with polyposis or Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC).
Methods: FDRs of 1196 Danish CRC patients diagnosed between 1995 and 1998 (baseline) were identified and the family history of cancer was assessed at baseline using Danish medical registries; 4182 FDRs without CRC from 1060 of the families were matched on age and gender with ten individuals from the general population and followed from baseline to 2010. Family history was updated with any new cancer event during follow-up.
Results: Using Cox proportional hazard modeling the risk estimates were: at least one relative with CRC: hazard ratio (HR) = 1.78 (95%CI: 1.45, 2.17), one relative with CRC diagnosed after the age of 50: HR = 1.68 (95%CI: 1.32, 2.14), one relative with CRC diagnosed before the age of 50: HR = 1.86 (95%CI: 0.70, 4.94), and multiple affected relatives: HR = 2.04 (95%CI: 1.38, 3.00).
Conclusion: Although the overall risk in FDRs of CRC patients in our study was comparable with the results of previous studies, the risk in families with multiple relatives with CRC or one CRC patient diagnosed young may be lower than reported previously.

1. Introduction

Colorectal cancer (CRC) is one of the most heritable cancers in humans. High-risk monogenic syndromes, such as Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), account for 2–5% of CRC cases [1,2]. In two meta-analyses, the increased CRC risk was estimated to be two-fold in first-degree relatives (FDRs) of CRC patients, rising to three- to four-fold in families where multiple FDRs were affected or the patient with CRC was diagnosed at a young age [3,4].

Most studies have ascertained family history of CRC by self-report. Monogenic high-risk syndromes account for a small portion of CRC cases; however,including families with the syndromes in studies of familial risk may lead to overestimation of the risk for FDRs in families free of these syndromes. Nonetheless,in most of the studies investigating familial CRC, monogenic syndromes have not been excluded before estimation of the risk in FDRs. In genetic counseling,the high-risk families can be identified by family history and/or genetic testing. An accurate risk estimate of CRC in families free of high-risk syndromes is required to counsel correctly the many persons with a less severe family history.

We estimated the risk of CRC in FDRs to CRC patients in a prospective cohort study involving families free of monogenic high-risk syndromes such as Lynch syndrome/HNPCC or FAP. The risk status of the families was set at the time of diagnosis of the

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proband and was continuously updated with any new familial events of CRC or other HNPCC-related cancers.

2. Material and methods

2.1. Study population and design

This was a matched cohort study including FDRs to patients (probands) diagnosed with primary CRC in the period November 1995 to October 1998.

2.2. The CRC probands

The probands were originally included in a study describing the frequency of HNPCC in Denmark [1,5,6]. All patients diagnosed with primary CRC in four Danish counties during this period were included. The counties had a population of 1,350,000 (26% of the Danish population). At baseline (time of CRC diagnosis) the probands completed a questionnaire ascertaining the number of FDRs, as well as cancers and age at diagnosis in the FDRs. If CRC was reported among the FDRs, an additional questionnaire to ascertain affected second-degree relatives was added. Among 1328 eligible patients, 1200 (90%) completed the questionnaire. For interviewees with a family history fulfilling the HNPCC Amsterdam I or II criteria [7] or where HNPCC was suspected (see supplementary table), mutations in mismatch repair (MMR) genes were screened for on blood samples from the proband.

2.3. Identification of FDRs

For each proband, the expected number of FDRs was known from the questionnaire. In the present study, we identified these FDRs with name, date of birth, and unique personal identifier (CPR number, see below) if possible. If more than one proband was identified per family, the proband diagnosed earliest was counted as proband and the subsequent cases were counted as FDRs with events in the follow-up period.

2.4. The Danish civil registration system

Since April 1st 1968, all Danish citizens are registered in the Danish civil registration system (DCRS) with a unique CPR number [8]. The system contains information on date and parish of birth, date of immigration or emigration, and date of death. Parents are linked to children if parents and children were living together in 1968 or later. The CPR number enables unambiguous data linkage between Danish medical registries.

2.5. The national archives

The children of the probands were mostly linked to the proband in the DCRS. However, for many of the families there was no link to parents and siblings in the system. We traced these relatives using documents in the national archives.

For probands born in Denmark, parents were identified by looking up the proband's date of birth in church books. For families with uncommon last names, the DCRS was searched for individuals with this name. Candidates were verified as siblings/children using the church books. In many cases, a combination of church books, censuses and population registry cards was used. For patients born in small parishes, it was feasible to find the siblings/children in the church book, whereas censuses and population registry cards were more useful for patients born in the bigger cities. In the early 1900s, censuses were conducted every 5th year and listed all citizens per household on the date of the census. Population registration cards, an early edition of the DCRS, were mandatory from 1924. The cards list families together and were continuously updated when families expanded or moved.

2.6. Follow-up and comparison cohorts

At baseline, FDRs alive, living in Denmark, and with no record of CRC were included in the follow-up cohort. A comparison cohort was created matching each FDR in the follow-up cohort on gender and year of birth with ten individuals from the background population with no history of CRC using DCRS. History of CRC was assessed using the medical registries listed below.

2.7. Cancer assessment

In the original study, attempts were made to verify all questionnaire-reported cases of CRC, other HNPCC-related cancers included in the Amsterdam II criteria, and abdominal cancers among FDRs through medical journals, death certificates, or the Danish cancer registry [3–5]. In the present study, FDRs with CPR numbers and the comparison cohort were linked to the Danish cancer registry and the Danish national registry of patients to retrieve information about all CRC and other HNPCC-related cancers included in the Amsterdam II criteria. Verified cancers among the FDRs diagnosed before baseline were constituted as the prevalent cancers. Diagnoses after baseline were counted as events during the follow-up. The Danish cancer registry has recorded all incident cases of malignant neoplasms since 1943 using the 7th edition of the International Classification of Disease (ICD7) until 1977 and thereafter the ICD10. The Danish national registry of patients holds information on all hospitalizations, using ICD8 codes of diagnoses (1977–1992) and ICD10 (1993–present) [9,10].

2.8. Family history of CRC as exposure

The prevalent cancer diagnoses at baseline were used when classifying the risk status of a family. High-risk families were defined as families with a detected MMR mutation, families fulfilling the HNPCC Amsterdam criteria, and families where a monogenic polyposis syndrome was likely. To increase the likelihood of identifying individuals with a monogenic high-risk predisposition or who had been offered screening because of a suspected risk, CPR numbers of probands, FDRs, and the comparison cohort were linked to the Danish polyposis register (DPR) and the Danish HNPCC register. The DPR and the HNPCC register have registered Danish polyposis families and Lynch/HNPCC families since 1971 and 1991, respectively [11,12]. The HNPCC register also holds information on families that do not meet the Amsterdam criteria, but where monogenetic risk of CRC is suspected and screening has been offered. Further, in 2005 the Danish association of surgeons suggested colonoscopy surveillance in what they termed "moderate-risk families": i.e., families with one individual diagnosed with CRC before the age of 50 or two FDRs with CRC. Such families are also registered in the HNPCC Register.

2.9. Risk groups

Risk group I included families with only the proband diagnosed with CRC and age at diagnosis 50 years or more. Risk group II included families with only the proband diagnosed with CRC, and age at diagnosis below 50 years. Risk group III included families with two or more FDRs, including the proband, diagnosed with CRC. For families in risk group III with CRC only in the proband and a parent, the other parent was assigned to risk group I or II depending on the age of diagnosis in the proband. During follow-

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up, the risk status of a family and the corresponding members of the comparison cohort was changed on the date of diagnosis of any relevant new cancer.

2.10. Follow-up

During the entire follow-up period mass screening for CRC was not recommended in Denmark. We excluded families fulfilling the monogenic high-risk criteria, since FDRs in these families were referred to colonoscopy surveillance programs by the end of the original study. No surveillance was offered to families in risk groups I–III.

The FDR cohort and comparison cohort were followed from baseline until either a CRC event, family changing status to high risk, registration of the family in the DPR or the HNPCC register with a diagnosis causing surveillance (including those registered as "moderate-risk families" after 2005), death, emigration, or the end of the follow-up (December 31th 2010), whichever came first.

2.11. Statistical analysis

We computed the frequency and proportion of the families and FDRs within categories of demographic and other descriptive variables. We calculated the frequency of CRC within risk groups, along with person-time at risk. Cox proportional hazard modeling was used to estimate the hazard ratios (HRs) with 95% confidence intervals (95%CIs) to investigate the risk of CRC in the FDRs compared to that in the comparison cohort. FDRs from the same family were regarded as clusters. We had no information on family relations in the comparison cohort; thus these individuals were considered independently of each other. To examine whether the CRC risk varied with the severity of the family history or age at CRC diagnosis in the proband, stratified analyses were made on risk groups. Further, we explored the proportion FDRs and individuals in the comparison cohort having at least one colon endoscopy performed from baseline to end of follow-up. Statistical analyses were performed using STATA (v11.0, StataCorp LP, College Station, TX, USA) and SAS (v9.2, SAS Institute Inc., Cary, NC, USA).

2.12. Ethical approval

The study was approved by the Danish Data Protection Agency, journal no.: 2014-41-2882.

3. Results

Four families each had two members diagnosed with CRC in the period November 1995 to October 1998, reducing the number of families to 1196. The 1196 probands originally reported having 9680 FDRs in total; 7880 (81%) FDRs were identified (Table 1). We found 252CRCs and 58 other HNPCC-related cancers among the FDRs before baseline. The characteristics of the families are shown in Table 2. Family size varied, with the smallest families in risk group II and in the high-risk group. In risk group II, FDRs were younger and a higher proportion of parents were included in the follow-up than in risk groups I and III (Table 3). Twenty-six (2.2%) families were identified as high-risk families at baseline: 22 families fulfilled the Amsterdam II criteria or had an MMR mutation, and in four families a monogenic polyposis syndrome was likely. According to the HNPCC Register, one further family not completely fulfilling the Amsterdam criteria had been offered surveillance. FDRs in these 27 families were excluded from follow-up. Further FDRs who were dead at baseline were excluded, leaving 4182 FDRs eligible to enter the follow-up cohort (Fig. 1). These 4182 FDRs originated from 1060 families.

We identified 113 cases of CRC among the FDRs and 630 cases in the ten-fold larger comparison cohort from baseline (1995–1998) through 2010 (Table 4). The mean follow-up time was 11.2 years in the cohort of FDRs and 11.1 years in the comparison cohort. Eighty-five families changed risk group because of an event of CRC or other HNPCC-related cancer. Three of these families changed status to high-risk, which terminated their follow-up; 77 families were registered in the Polyposis Register or the HNPCC Register during follow-up, and of these one family had FAP and five had HNPCC. Seventy-one families were either suspected of monogenic CRC risk or fulfilled the "moderate-risk" criteria for surveillance introduced in 2005.

We found an association between being an FDR to a CRC patient and the risk of CRC (HR = 1.78, 95%CI 1.46, 2.17) (Table 4). Stratifying by risk group, the association was strongest for FDRs with multiple relatives diagnosed with CRC (risk group III; HR = 2.04, 95%CI 1.38, 3.00), whereas the hazard ratios for risk groups I and II were closer to the overall risk (risk group I, HR = 1.68, 95%CI 1.32, 2.14) and (risk group II, HR = 1.85, 95%CI 0.70, 4.94).

Of the FDRs, 15% had at least one colon endoscopy during the follow-up compared to 10% of the individuals in the comparison cohort. It was not possible to distinguish whether these procedures were diagnostic or screening endoscopies. Among individuals without a CRC diagnosis, the proportions were 14% and 9.8%, respectively.

Table 1
Characteristics of 1196 probands diagnosed with colorectal cancer 1995–1998.

Males, *n* (%)	593 (50)
Females, *n* (%)	603 (50)
Age, years at diagnosis, median (interquartile range)	69 (62–78)
Type of CRC, *n* (%)	
Colon	733 (61)
Rectum	463 (39)

Number of FDRs, *n* (%)	Questionnaire reported[a] (ref.)	Identified in registries
Total number of FDRS	9680	7880 (81)
Fathers	1196	1115 (93)
Mothers	1196	1141 (95)
Siblings	4410	3247 (74)
Children	2878	2377 (83)
Probands with FDR in the follow-up cohort	Not reported	1060
FDRs in the follow-up cohort[b]	Not reported	4182

Abbreviations: CRC, colorectal cancer; FDR, first-degree relative.
[a] Probands is assumed to have a mother and a father. The number of siblings and children are the numbers reported by the probands at baseline.
[b] FDRs alive, living in Denmark, and with no record of CRC diagnosis at the time of the proband's diagnosis, FDRs from high risk families excluded.

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Table 2
Baseline characteristics of the 1196 families by risk status based on verified cancer diagnoses.

	Risk group			
	I[a] (1 CRC > 50 Y)	II (1 CRC < 50 Y)	III (>2 CRC)	High[b]
Families, *n* (%)	910 (77)	64 (5.4)	196 (16)	26 (2.2)
Number of FDRs identified, *n* (%)[c]				
Total	5816 (79)	348 (88)	1543 (87)	173 (96)
Fathers	837 (92)	60 (94)	193 (98)	25 (96)
Mothers	859 (94)	60 (94)	196 (100)	26 (100)
Siblings	2,304 (70)	109 (77)	753 (85)	81 (96)
Children	1,816 (83)	119 (96)	401 (79)	41 (93)
Family size[d], *n* (%)[e]				
Small (<4 FDRs)	47 (5.2)	9 (14)	9 (4.8)	3 (12)
Medium (5–12 FDRs)	705 (78)	54 (84)	138 (71)	19 (72)
Large (>13 FDRs)	152 (17)	1 (1.6)	48 (25)	3 (12)
Information on family size missing	6 (<1)	0 (0)	1 (<1)	1 (3.8)
Family size, mean (min–max)	9.1 (3–21)	7.2 (3–16)	10.1 (3–24)	8.0 (3–15)

Abbreviations: CRC, colorectal cancer.
[a] Families with no identified FDRs to the proband are included in risk group I.
[b] Families with a monogenic polyposis syndrome or hereditary nonpolyposis colorectal cancer/lynch syndrome.
[c] (%) = percentage of questionnaire-reported number of FDRs.
[d] Family size including the proband.
[e] (%) = percentage of total number of families in risk group.

Table 3
Baseline characteristics of first degree relatives (*n* = 4182) to 1060 Probands included in the follow-up.

	Risk group		
	I (1 CRC > 50 Y)	II (1 CRC < 50 Y)	III (>2 CRC)
Total, *n* (%)[a]	3166[b](75)	295 (7.0)	721 (17)
Families included *n* (%)[c]	811 (89)	63 (98)	186 (95)
Age at baseline (mean, interquartile range)	53 (38–39)	38 (17–56)	55 (39–71)
Age groups, *n* (%)			
0–24 years	113 (3.6)	114 (39)	28 (3.9)
25–49 years	1461 (46)	87 (29)	302 (42)
50–74 years	1136 (36)	71 (24)	269 (37)
75+ years	456 (14)	23 (7.8)	122 (18)
Family relation to proband, *n* (%)[c]			
Parents	126 (4.0)	75 (25)	2 (<1)
Siblings	1326 (42)	101 (34)	344 (48)
Children	1714 (54)	119 (40)	375 (52)
Sex, *n* (%)[c]			
Males	1515 (48)	147 (50)	356 (49)
Females	1651 (52)	148 (50)	365 (51)

Abbreviations: CRC, colorectal cancer.
[a] (%) = percentage of first degree relatives in each risk group.
[b] Including ten parents from families in risk group III, for which the risk status is based on the diagnosis in the proband and the other parent of the proband.
[c] (%) = percentage of the total number families in each risk group.

4. Discussion

We investigated familial risk of CRC in a large prospective cohort study which excluded families diagnosed with a known monogenic high risk. CRC incidence was measured among 4182 FDRs to CRC patients and compared with the incidence in a cohort selected from the general population matched on age and gender. We found an increased risk of CRC of almost two-fold in FDRs to CRC patients, consistent with previous meta-analyses [3,4]. However, the relative risks in families with either multiple CRC patients or one CRC patient diagnosed young were appreciably lower than previously reported from studies that did not systematically exclude families with a monogenic high risk.

Denmark has universal public health care, and the CRC probands in our study were consecutively included and had a very high response rate on the original questionnaire (90%), reducing the potential for selection bias. Our study is one of few prospective cohort studies covering this topic, the only one to continuously update family history during follow-up, and the only one to systematically exclude families with monogenic CRC syndromes both before and during follow-up. The study used cancer diagnoses from medical registries when describing the family history, which minimizes the risk of misclassification due to recall bias. Even though several studies have shown that the validity of self-reported CRC in relatives is high [6,13], studies including register-based cancer diagnoses of all relatives, regardless of reported history of cancer, found that CRC is often underreported in relatives [14,15]. We identified 81% of all FDRs. The percentage of identified FDRs was lower in risk group I than in the other risk groups. This missing information may have caused some misclassification of families with two or more CRC cases or high-risk families into risk group I. If so, this misclassification should bias the relative risk estimate upwards in risk group I, but would not affect the risk estimates of the other two groups.

To reduce the bias caused by surveillance endoscopies, we excluded families registered in the Danish Polyposis or HNPCC

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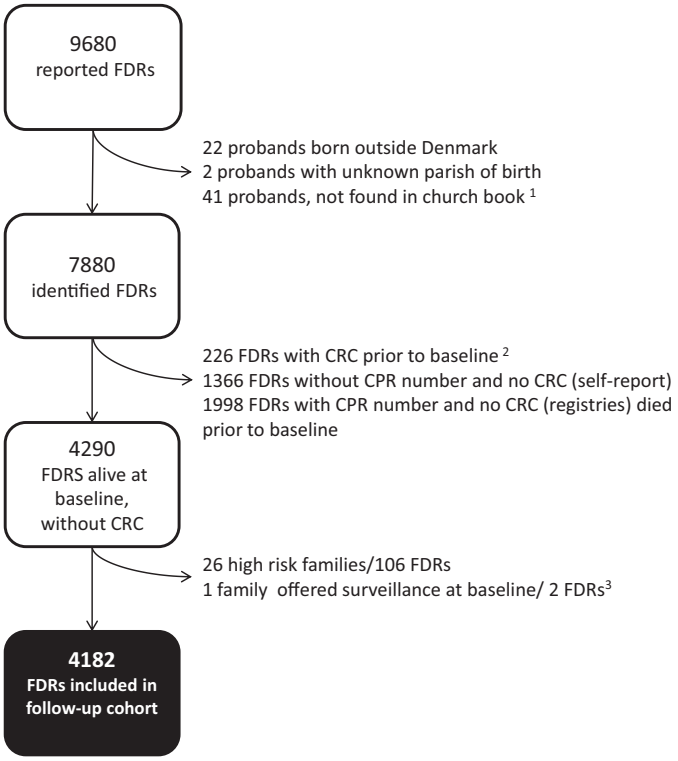

Fig. 1. Flowchart showing the identification of the FDRs in the cohort.
[1]If there was any FDRs identified, these were included in the study.
[2]Family history of CRC and HNPCC-related cancer was used to seperate into risk groups
[3]Family not fulfilling the Amsterdam criteria completely, but surveillance was offered according to the Danish HNPCC registry.
Abbreviations: CRC, colorectal cancer; FDR, first degree relative; CPR number, unique personal identifier; HNPCC, hereditary non-polyposis colorectal cancer.

Table 4
Hazard ratios for colorectal cancer among 4182 first degree relatives to Danish colorectal cancer patients compared to the matched cohort (1995–2010).

	n[a]	CRC cases	Person time/years	HR	95% CI
Total[b]					
FDRs	4182	113	47,423	1.78	1.45, 2.17
Comparison cohort	41,765	630	469,796	1	
Risk group I (1 CRC > 50 Y)					
FDRs	3166	76	34,485	1.68	1.32, 2.14
Comparison cohort	31,614	445	339,670	1	
Risk group II (1 CRC < 50 Y)					
FDRS	295	5	3319	1.86	0.70, 4.94
Comparison cohort	2946	27	33,326	1	
Risk group III (>2 CRC)					
FDRS	721	32	9620	2.04	1.38, 3.00
Comparison cohort	7205	158	96,800	1	

Abbreviations: CRC, colorectal cancer; FDR, first-degree relative; HR, Hazard Ratios.
[a] Number in the group at baseline.
[b] After exclusion of high risk families.

registries, including those registered as "moderate-risk families" from 2005 and onwards. We cannot exclude the possibility that some families were classified as "moderate-risk" by a surgeon, without being registered, or that having a family history of CRC may have led to opportunistic screening among the FDRs included in our study. However, as most of the follow-up time of our study precedes 2005, when surveillance was first introduced by surgeons, most families would not have been aware of the surveillance recommendations. In addition, we found that only a small proportion of the FDRs and the comparison cohort underwent a colon endoscopy. Thus it is unlikely that our findings can be explained by differential screening rates.

In two meta-analyses of familial CRC from 2001 and 2006, similar risks were observed [3,4]. In the most recent meta-analysis, including 57 studies, the summary relative risk of CRC was 2.24 (95%CI 2.06, 2.43) for persons having at least one FDR with CRC [4]. We observed a hazard ratio of 1.78 (95%CI 1.46, 2.17). There is little overlap between the confidence intervals of these two estimates of effect.

Notable differences appeared among subgroups, but this should be viewed with caution because of the small numbers. If multiple relatives were affected, the relative risk estimated in the meta-analysis was 3.97 (95%CI 2.60, 6.06) and 3.55 (95%CI 1.84, 6.83) if the proband was diagnosed young, whereas we estimated hazard ratios of 2.04 (95%CI 1.38, 3.00) and 1.85 (95%CI 0.70, 4.94) in the present study. The study population of risk group II (one CRC <50 years) was rather young (mean age 38 at baseline); thus we cannot exclude the possibility that this group could have a higher cancer risk at older age. Only a few of the studies included in the meta-analyses have investigated the risk for persons with multiple affected FDRs or having one FDR diagnosed young, and none of the studies systematically excluded monogenic high-risk families. Monogenic high-risk syndromes may only account for up to 5% of all CRC cases, but these syndromes could account for 20–50% of CRC among families with multiple affected relatives or with relatives diagnosed young [16,17]. Thus, in families with CRC where a monogenic predisposition to CRC is excluded, the risk of CRC in FDRs has likely been overestimated. Two studies, not included in the meta-analyses, investigated the risk of CRC in FDRs to CRC patients diagnosed at young age. Jenkins et al. [18] found an almost three-fold risk: SMR = 2.7 (95%CI: 1.7, 4.1). In this study attempts were made to exclude high-risk families, though less systematically than in the present study. Out of 131 patients, mutation analysis was offered to 12 Amsterdam-II-positive families and 31 random patients. FDRs to six patients with MMR mutation were excluded. In contrast, Boardman et al. [19] excluded Lynch syndrome more systematically by including only FDRs to 278 patients diagnosed at a young age with microsatellite stable tumors, and found an RR = 1.65 (95%CI: 1.29, 2.07) consistent with the risk estimates of the present study: HR = 1.85 (95%CI: 0.70, 4.94).

5. Conclusion

We observed a lower risk in FDRs to one relative with CRC at the age of 50 or older (HR = 1.68, 95%CI 1.32, 2.14) than in the other non-monogenic risk groups; however, the difference between these risks was not substantial. The results from the meta-analyses have led health agencies to recommend more extensive screening in families with multiple affected relatives and families with one person diagnosed young than in families with less severe family histories [20,21]. With the caution that the FDRs in risk group II were younger than those in the other groups, the results of the present study indicate that this stratification may not be relevant. In conclusion, our data confirm previous findings that FDRs to CRC patients without a monogenic high-risk syndrome have an increased risk of CRC of approximately two-fold. The risk does not seem to be much influenced by the family history or age at diagnosis of the affected relatives.

Conflict of interest

The authors declare that they have no conflict of interest

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