Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia

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Context Vigorous physical activity is thought to increase risk of bleeds in children with hemophilia, but the magnitude of the risk is unknown.

Objective To quantify the transient increase in risk of bleeds associated with physical activity in children with hemophilia.

Design, Setting, and Participants A case-crossover study nested within a prospective cohort study was conducted at 3 pediatric hemophilia centers in Australia between July 2008 and October 2010. A total of 104 children and adolescent boys aged 4 through 18 years with moderate or severe hemophilia A or B were monitored for bleeds for up to 1 year. Following each bleed, the child or parent was interviewed to ascertain exposures to physical activity preceding the bleed. Physical activity was categorized according to expected frequency and severity of collisions. The risk of bleeds associated with physical activity was estimated by contrasting exposure to physical activity in the 8 hours before the bleed with exposures in two 8-hour control windows, controlling for levels of clotting factor in the blood.

Main Outcome Measures Association of physical activity and factor level with risk of bleeding.

Results The participants were observed for 4839 person-weeks during which time 436 bleeds occurred. Of these, 336 bleeds occurred more than 2 weeks after the preceding bleed and were used in the primary analysis of risk. Compared with inactivity and category 1 activities (eg, swimming), category 2 activities (eg, basketball) were associated with a transient increase in the risk of bleeding (30.6% of bleed windows vs 24.8% of first control windows; odds ratio, 2.7; 95% CI, 1.7-4.8, $P<.001$). Category 3 activities (eg, wrestling) were associated with a greater transient increase in risk (7.0% of bleed windows vs 3.4% of first control windows; odds ratio, 3.7; 95% CI, 2.3-7.3, $P<.001$). To illustrate absolute risk increase, for a child who bleeds 5 times annually and is exposed on average to category 2 activities twice weekly and to category 3 activities once weekly, exposure to these activities was associated with only 1 of the 5 annual bleeds. For every 1% increase in clotting factor level, bleeding incidence was lower by 2% (95% CI, 1%-3%; $P=.004$).

Conclusions In children and adolescents with hemophilia, vigorous physical activity was transiently associated with a moderate relative increase in risk of bleeding. Because the increased relative risk is transient, the absolute increase in risk of bleeds associated with physical activity is likely to be small.

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Hemophilia is a bleeding disorder that, if untreated, causes recurrent bleeding into joints and, eventually, hemophilic arthropathy and joint contracture.[1] The severity of hemophilia is classified according to levels of clotting factor in the blood, which are expressed as a percentage of normal values (severe <1%, moderate 1%-5%, mild >5%-40%). Before the introduction of plasma-derived and recombinant prophylactic clotting factors, children with hemophilia were advised against taking part in vigorous physical activity because physical activity was believed to increase the incidence of bleeds.[2]

Prophylactic injections of recombinant factor VIII have been shown in 2 randomized trials to reduce the risk of bleeds in children with hemophilia. One trial involving 65 participants (266 person-years) showed administration of 85 IU/kg per week reduced the incidence of all bleeds (intra-articular and extra-articular) by 82%.[3] The other trial that involved 45 participants (260 person-years) showed administration of 75 IU/kg per week reduced the incidence of all bleeds by 48%.[4] The clinical ef-

See also p 1480 and Patient Page.

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fects of lower doses have not been rigorously tested.[5]

The reduction in risk of bleeds conferred by prophylaxis may be such that the benefits of physical activity outweigh the risk of bleeds. However, the degree to which risk of bleeds is elevated by physical activity has not been determined. Information about risks associated with physical activity is needed to inform decisions about participation in physical activity and to optimize prophylactic schedules.

The primary aim of this study was to quantify the transient increase in risk of bleeding associated with vigorous physical activity in children with hemophilia. Secondary aims were to determine the induction period for a bleed caused by vigorous physical activity (ie, the time between physical activity and appearance of a bleed) and to determine the association between clotting factor level and risk of bleeds.

METHODS

This was a case-crossover study nested within a prospective cohort study. The case-crossover design enables quantification of risk associated with transient exposures. It is more efficient than cohort designs because it samples only cases and may be less exposed to selection bias than case-control designs because cases provide their own control data.[6] The study protocol has been published.[7] The study was approved by the University of Sydney Human Research Ethics Committee and by the ethics committees of recruiting sites. Parents or guardians of participating children gave written informed consent.

Participants

Children and adolescents between 4 and 18 years with moderate (factor VIII-IX level, 0.01-0.05 U/mL) or severe (factor VIII-IX level, <0.01 U/mL) hemophilia A or B were eligible for the study. In all, 104 boys from 3 of 5 pediatric hematology departments servicing eastern Australia between July 2008 and July 2010 participated in the study.

Procedures

Interviews were conducted by telephone with the child or adolescent or with the parent or guardian. The term *participant* is used to refer to the child, adolescent, or parent or guardian who was interviewed. The participant was the person who could most reliably report on physical activity exposure, occurrence of bleeding episodes, and clotting factor schedules. Participants were assured that all data would be treated as confidential and would not be conveyed to treating physicians.

Each child was monitored for up to 1 year following study entry to determine when bleeds occurred. A *bleed* was defined as "an episode of bleeding requiring treatment with clotting factor."[8] Participants were asked to notify researchers of bleeds. In addition, participants maintained a bleed diary. Furthermore, each participant received weekly short message service (SMS) messages (text messages) at a prespecified time each week to ascertain if a bleed had occurred in the past week. If no reply was received, messages were sent 24 and 48 hours later. If there was still no reply, the participant was contacted by telephone.

The participant was interviewed by telephone as soon as possible after a bleed. A bleed was considered to have occurred at the time it was first noticed, as determined by pain, tingling, or swelling in the affected region. The interviewer assisted the participant to describe all physical activities engaged in for the 3 days preceding the bleed. Although data were obtained on all physical activity in the 3 days before the bleed, the primary analysis used only data on physical activity in the 8-hour period immediately preceding the bleed (ie, in the bleed window) and the two 8-hour periods ending 24 hours (the first control window) and 48 hours (the second control window) before the bleed. Information was also sought about the timing and dose of clotting factor injections in the previous week.

The same interview procedures were followed for all bleeds unless a bleed occurred within 2 weeks of a previous bleed. In that circumstance, an interview was not conducted because pilot testing suggested it was too onerous for participants to be interviewed more than once per fortnight and frequent interviewing could compromise quality of reporting. Bleeds that occurred within 2 weeks of a previous bleed were used to estimate incidence of bleeds but were not used to quantify the risk of bleeds associated with physical activity. We refer to the subset of bleeds that occurred more than 2 weeks after the preceding bleed as *study bleeds*.

For each participant, a *pseudobleed* time and date were randomly generated during the study period. The participant was contacted by telephone at the time of the pseudobleed and asked the same questions about exposure to physical activity in the preceding 3 days as were asked following study bleeds. Data from these random interviews were divided into data from an 8-hour pseudobleed window immediately preceding the pseudobleed and two 8-hour pseudocontrol windows ending 24 and 48 hours before the pseudobleed. The data were used to check quality of estimates of exposure to physical activity obtained in control windows and the validity of using control windows from the days preceding the bleed.

Data Analysis

Each episode of physical activity was broadly categorized using a modification of the taxonomy devised by the American National Hemophilia Foundation.[9] The taxonomy categorizes activities according to expected frequency and severity of collisions (eTable 1 available at http://www.jama.com). Category 1 activities are activities in which significant collisions are not expected (eg, swimming). Category 2 activities are those in which significant collisions might occur (eg, basketball). Category 3 activities are those in which significant collisions are inevitable (eg, wrestling). The tax-

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onomy was used to categorize the highest exposure to physical activity in the 8 hours preceding the bleed and in the same 8 hours 1 and 2 days preceding the bleed. The exposure level assigned to each window was the highest level of exposure occurring during that window.

The main potential confounder in the case-crossover analysis is the level of clotting factor, since factor injections are expected to reduce risk of bleeds and injections may be timed to precede high risk activities. Consequently, clotting factor levels were estimated and adjusted for in the analysis. Clotting factor level at the time of the first instance of the highest exposure in each window was estimated using a single compartment pharmacokinetic model based on timing and dose of the last factor injection, hemophilia severity, body weight, in vivo recovery, and factor half-life.[10-13] Single compartment pharmacokinetic models have been widely used to study clotting factor levels in hemophilia and approximate measured factor levels.[11,14-16]

Conditional logistic regression was used to estimate the relative increase in risk of bleeds associated with category 2 or 3 activities (compared with the reference condition of inactivity and category 1 activities) adjusted for clotting factor levels. Odds ratios (ORs) were derived using both control windows: ie, both the 8-hour window ending 24 hours prior to the bleed and the 8-hour window ending 48 hours prior to the bleed. The OR generated by conditional logistic regression is an incidence rate ratio, even if the incidence of bleeds is high.[17,18] Because observations were not independent (many participants experienced more than 1 bleed), confidence intervals were calculated with nonparametric bootstrap methods that allowed for clustering by subject.

The regression model also provided an estimate of the effect of clotting factor level on risk of bleeds. The model used in the primary analysis can be rearranged to calculate the dose that would be required to elevate factor levels sufficiently to achieve a target percentage reduction in bleeds risk, R. The rearranged equation is:

$$dose = [\ln(\{100 - R/100\})] / (IVR \times d)$$

for which IVR is the in vivo recovery and d is the natural log of the OR associated with clotting factor levels (ie, $d = ln(0.98) = -0.016$).

By extending the logic of case-control studies[18] to case-crossover studies, it can be shown that when control windows are selected without regard to exposure, the OR in a case-crossover study is actually an incidence rate ratio. The total number of bleeds experienced in a year is the exposure- and risk-weighted sum of the number of bleeds associated with periods of inactivity and periods of exposure to category 2 and 3 activities. That is

$$Number\ of\ bleeds\ per\ year_i = (t_1 \times b_i) + (t_2 \times OR_2 \times b_i) + (t_3 \times OR_3 \times b_i)$$

for which t_1, t_2, and t_3 are the proportions of time spent inactive and engaging in category 2 and 3 activities, respectively; OR_2 and OR_3 are the ORs associated with exposure to category 2 and 3 activities, and b is the base rate of bleeds. The subscript i means "for child i." Given values of t_1, t_2, and t_3 and the number of bleeds for a particular child, this equation can be used to calculate the value of b_i for that child. The absolute number of bleeds per year attributable to category 2 and 3 physical activity for that child is then

$$(t_2 \times OR_2 \times b_i) + (t_3 \times OR_3 \times b_i).$$

The primary analysis assumed the induction period for bleeds caused by physical activity is less than 8 hours. The length of the induction period was explored by examining histograms of time elapsed between each bleed and the preceding occasion of physical activity.

The study was powered for the primary analysis, which involved estimation of the risk of bleeding associated with physical activity. The approach to calculating sample size has been described.[7] First, we calculated the sample size necessary for a conventional paired case-control study[19] to provide an 80% probability of detecting an OR of 2.5 by assuming (1) a 2-tailed $\alpha = .05$, (2) 20% of participants would be exposed to exercise in the control period, and (3) a correlation between exposures in the case and control period of 0.5. The relatively large risk (OR, 2.5) was justified because the risk is only transient. That sample size was divided by 4 because it was anticipated that each participant would experience, on average, about 4 bleeds. This estimate was based on the recruiting sites' records of bleeding rates among patients who would have been eligible for the study and data from recent reports of children receiving prophylaxis.[3,12] Then, to allow for the lack of independence among repeated bleeds, the sample size was inflated by a design factor that was a function of the estimated average of 4 bleeds per participant and the estimated 0.2 maximum intraclass (intraparticipant) correlation.[20] This yielded a sample size of 336 bleeds. Consequently, we specified in advance that the study would be terminated after the 336th study bleed. Data analyses were conducted independently by 2 analysts using Stata statistical software version 11.1 (StataCorp Inc).

A series of sensitivity analyses was conducted. First, the analysis was repeated with missing data imputed using multiple imputation. Then an analysis was conducted in which waking bleeds (bleeds first noticed by the participant on waking in the morning) were excluded from the analysis. The rationale was that it is not known when the child would first have noticed symptoms of the bleed had he not been asleep. Another analysis excluded data from participants with a history of high titer inhibitors (>0.5 BU/mL). Further analyses used pseudocontrol windows rather than control windows, and investigated effects on parameter estimates of varying the length of bleed and control windows from 1 to 12 hours.

RESULTS

Flow of Participants Through the Study

Two hundred five children living in the mainland Eastern states of Australia met

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the eligibility criteria.[21] Of these, 169 were registered at the recruiting clinics. All children who attended the recruiting clinics during the recruitment period were invited to participate. Those registered but not attending clinics during the study period or who were not contactable were not invited to participate. Once the target of 336 bleeds appeared likely to be achieved recruitment of participants ceased, so 117 children were invited to participate of whom 104 consented. Thus 89% of those invited and 51% of those eligible participated.

The 104 children were followed up for 4839 person-weeks. The median duration of follow-up was 52 weeks (interquartile range [IQR], 52-52 weeks; range, 14-52 weeks). Not all were followed up for 52 weeks because the study was terminated when the 336th bleed was recorded. Short message service (text) replies were received for 4201 weeks, so there was 87% ascertainment of bleed status. Median time between a bleed and interview was 6 days (IQR, 4-8 days). For practical reasons it was not possible to conduct telephone interviews for 7 bleeds, so interviews were conducted for 329 study bleeds (98%). Complete exposure data were obtained for all 329 bleeds. Characteristics of participants appear in TABLE 1.

Patterns of Bleeds

There were 436 bleeds, of which 336 were study bleeds (ie, bleeding episodes without another bleeding episode in the preceding 2 weeks). Eighty-eight participants (84%) reported at least 1 bleed. The incidence rate was 5.4 bleeds per person-year (FIGURE 1).

The median incidence rate (bleeds/year) was 4.9 (IQR, 2.4-12.0) for participants with moderate hemophilia and 3.0 (IQR, 1.1-7.4) for those with severe hemophilia. The median incidence rate was 4.3 (IQR, 2.6-14.2) for participants receiving on-demand therapy and 3.0 (IQR, 1.1-7.4) for those receiving prophylaxis.

The most frequent sites of bleeding were the knee (15%), ankle (14%), and elbow (10%). Less frequent sites were the hand (9%), foot (9%), arm (7%), thigh (6%), leg (7%), shoulder (5%), head (5%), trunk (5%), wrist (3%), forearm (3%), nose (2%), neck (1%), and hip (1%). There was no evidence that rate of bleeds varied with week of year ($P=.21$; Figure 1B) or day of week ($P=.18$), but there were large variations with time of day (Figure 1C). The frequency of bleeds was highest between 7 and 8 AM and 3 and 4 PM, coinciding with the periods before and after school.

Exposure to Physical Activity and Clotting Factor

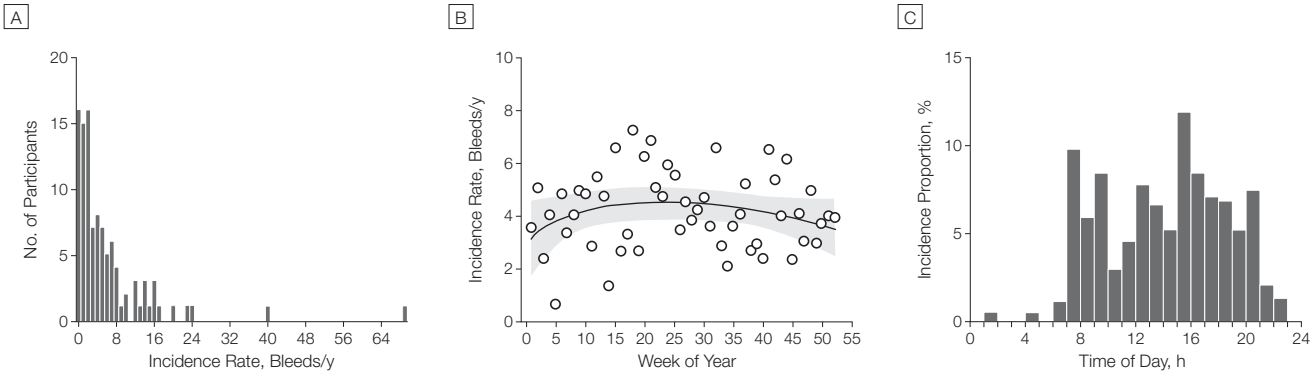
For the 329 study bleeds for which interviews were conducted, there was exposure to category 2 activity in 30.6% of bleed windows, 24.8% of first control windows, and 21.4% of second control windows. There was exposure to category 3 activity in 7.0% of bleed windows, 3.4% of first control windows, and 4.6% of second control windows. For

Table 1. Characteristics of Study Participants (N = 104)

	No. (%) of Participants
Age, mean (SD), y	9.5 (4.0)
Range	4-18
Hemophilia type	
A	85 (81.7)
B	19 (18.3)
Hemophilia severity	
Moderate	18 (17.3)
Severe	86 (82.7)
Treatment	
Prophylaxis	89 (85.6)
On-demand	15 (14.4)
Target joints[a]	45 (43.3)
Inhibitors	13 (12.5)
Weekly prophylactic dose in IU/kg[b]	
Factor VIII, median (IQR)	107 (84-151)
Factor IX, median (IQR)	99 (63-150)

[a] For the purposes of this study, joints were considered to be target joints if the child or parent reported recurrent bleeding in the same joint.
[b] Prophylactic doses are for the 75 participants receiving prophylactic factor VIII supplementation and 14 participants receiving prophylactic factor IX supplementation.

Figure 1. Patterns of Bleeding



A, Frequency distribution of incidence rates of all 436 bleeds. The first bin includes 0 bleeds/year. B, Incidence rate of bleeds by week of year. The curve is a second-degree fractional polynomial regression. There is no evidence that the rate of bleeds varied with week of year ($P=.21$). The shaded area represents 95% confidence intervals. C, Incidence proportion of study bleeds by time of day. The first bin includes 12 AM and extends to before 1 AM.

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44% of bleeds, participants could recall an injury that they perceived to have caused the bleed.

At the first instance of the highest level of activity in each window, median clotting factor levels were estimated to be 3% of normal levels for all 3 windows.

Association of Physical Activity and Factor Level With Risk of Bleeding

The OR was 2.7 (95% CI, 1.7-4.8, $P<.001$) for category 2 activity and 3.7 (95% CI, 2.3 to 7.3, $P<.001$) for category 3 activity. The OR for the level of clotting factor in the blood was 0.980 (95% CI, 0.965-0.992). The level of clotting factor is a continuous variable, so the OR of 0.980 implies that the incidence rate was lower by 2% for every 1% increase in clotting factor level (FIGURE 2).

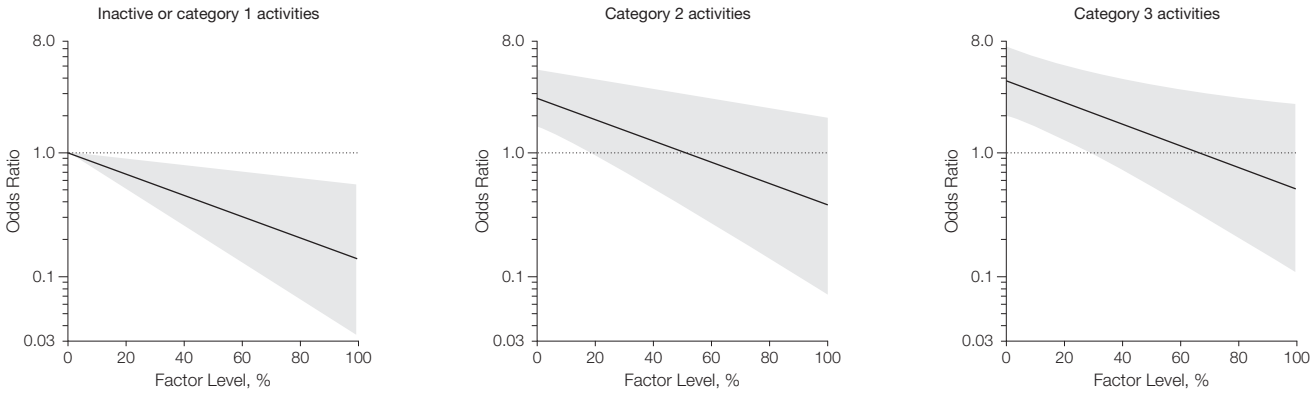
The OR for clotting factor level can be used to estimate the amount of factor required to produce a target reduction in risk of bleeds at the time of the injection. Equation 1 shows, for example, that 22 IU/kg of clotting factor VIII is estimated to be required to produce a 50% reduction in the risk of bleeds at the time of the injection (assuming an in vivo recovery of 2.0[11,12]). The level of clotting factor in the blood and the protective effect of clotting factor injections decays with time after injection.

The OR of 2.7 for category 2 and 3.7 for category 3 physical activities means that, for most children, the absolute increase in risk associated with physical activity is low. For example, for a boy who bleeds 5 times annually and is exposed, on average, to category 2 activities in two 8-hour epochs and to category 3 activities in one 8-hour epoch each week, exposures to these activities are associated with 1 of the 5 bleeds experienced each year. For most children, $(t_1 \times b_i) >> (t_2 \times OR_2 \times b_i) + (t_3 \times OR_3 \times b_i)$, implying that most bleeds are not associated with physical activity.

Induction Time and Effect of Window Duration

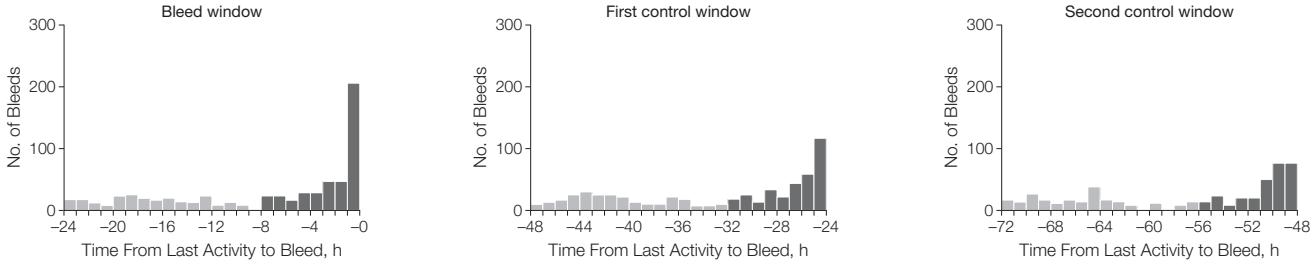
Exposure to physical activity in the hour preceding bleeds was greater in the bleed window than in control windows, suggesting most bleeds associated with physical activity are apparent within an hour (FIGURE 3).

Figure 2. Odds Ratios for Bleeds by Clotting Factor Level and Activity Level



Participants who were inactive or engaged in category 1 activities reported 229 bleeding events; engaged in category 2 activities, 84 events; and engaged in category 3 activities, 16 events. Rates are referenced to the rate of bleeding while inactive or engaging in category 1 activity with a factor level of 0 (horizontal dotted line). The shaded regions represent 95% CIs. The curves and the confidence intervals have been constructed from the conditional logistic regression model. Category 1 includes activities that do not involve expected collisions (eg, swimming); category 2, activities in which significant collisions might occur (eg, basketball); and category 3, activities in which significant collisions are inevitable (eg, wrestling).

Figure 3. Time Elapsed Between Bleed and Preceding Category 2 or 3 Activity



The first bin in the bleed window includes –24 hours and extends to less than –23 hours. The same convention is used in the first and second control windows. The 8-hour exposure windows used in the primary analysis are dark gray.

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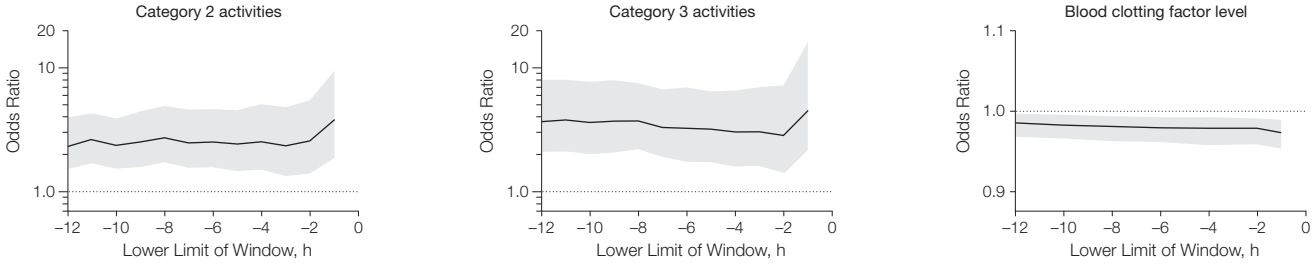
Figure 4. Effect of Window Duration on the Estimated Odds Ratios for Each Activity Category



Effect of window duration on estimates of odds ratios (329 study bleeds; 229 after exposure to category 0 and 1 activity, 84 after exposure to category 2 activity, 16 after exposure to category 3 activity). Shaded regions are 95% CIs. Odds ratio for category 2 activities (reference category is category 0-1 activity). Odds ratio for category 3 activities (reference category is category 0-1 activity). Odds ratio for blood clotting factor level (the ratio of odds associated with every 1% increase in clotting factor level). See Figure 2 legend for definition of activity categories.

Random Interviews

Random interviews were conducted for 99 of the 104 participants. Five participants could not be contacted at the time of their randomly generated interview. For the 99 random interviews, there was exposure to category 2 activity in 15.2% of pseudobleed windows, 21.2% of first pseudocontrol windows, and 19.2% of second pseudocontrol windows. There was exposure to category 3 activity in 2.0% of pseudobleed windows, 2.0% of first pseudocontrol windows, and 2.0% of second pseudocontrol windows.

Sensitivity Analyses

When the data were reanalyzed with multiple imputation, or excluding waking bleeds, or excluding patients with inhibitors, the results were essentially unchanged (eTable 2 available at http://www.jama.com). Parameter estimates were insensitive to variation of the length of bleed and control windows, at least for window durations greater than 1 hour (FIGURE 4). Estimates of risk obtained using pseudocontrol windows rather than control windows yielded similar estimates (OR, 2.8 for category 2 activities; OR, 4.1 for category 3 activities) to those obtained in the primary analysis (TABLE 2).

Table 2. Odds Ratios for Exposure to Physical Activity and Clotting Factor Level[a]

	Estimate (95% CI)	
Category	Primary Analysis, Using Control Windows	Sensitivity Analysis, Using Pseudocontrol Windows
Activity category		
2	2.7 (1.7-4.8)	2.8 (1.5-6.1)
3	3.7 (2.3-7.3)	4.1 (1.6-22.5)
Clotting factor level	0.980 (0.965-0.992)	Not estimated

[a] Results from 2 analyses are shown. The primary analysis used exposure data from bleed and control windows whereas the sensitivity analysis used exposure data from bleed and pseudocontrol windows. The sensitivity analysis was not adjusted for clotting factor levels. Rates are referenced to the rate of bleeding while inactive or engaging in category 1 activity with a factor level of 0.

COMMENT

This study provides estimates of the risk of bleeding associated with vigorous physical activity in children with hemophilia. Category 2 physical activity was associated with a transient increase in the risk of bleeding (OR, 2.7) and category 3 physical activity was associated with a greater transient increase in risk (OR, 3.7). Bleeding incidence was lower by 2% for every 1% increase in clotting factor level. Most bleeds associated with physical activity were manifest within an hour of activity.

Comparison With Other Studies

Two studies have examined the relationship between physical activity and bleeding outcomes in children with hemophilia. Ross and colleagues[22] retrospectively examined records of 37 children with severe hemophilia receiving prophylaxis and found that level of impact of physical activity did not predict joint outcome. Tiktinsky and colleagues[23] studied 44 children with hemophilia not receiving prophylaxis and found no correlation between number of bleeds and level of physical activity, although the group that engaged in strenuous exercise had a higher proportion of traumatic bleeds. These studies involved between-participant comparisons so are potentially exposed to selection bias.

A cohort study involving children and adults with hemophilia estimated that the risk of bleeds increased by 1.4% to 2.2% (depending on age) for every additional hour per week that factor VIII levels were less than 1%. In that study clotting factor levels were calculated using pharmacokinetic measures obtained from each child. However the estimate of effect of clotting factor dose was based on between-participant comparisons that could be subject to selection bias, and there was no control for confounding by physical activity.[24]

Strengths and Limitations of the Study

Half of all eligible children and adolescents with hemophilia from the main-

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land Eastern states of Australia participated. Near-complete data were obtained on exposures with a high level of follow-up of outcomes.

The main limitation of this study is the potential for recall bias. At issue is whether participants were more able to recall physical activity on the day of the bleed than on the second or third days before the bleed. Data from the random interviews show that levels of exposure to physical activity reported in the window preceding a randomly selected time were similar to those reported on the preceding 2 days, suggesting participants were as able to recall physical activity data on the preceding 2 days as they were on the day of the bleed.

Another potential limitation arises because participants self-reported exposures and outcomes but were not explicitly blinded. To minimize the possibility of participants' anticipating the study hypotheses and responding accordingly, participants were not told the length of bleed and control windows. Failure to report bleeds may also be a potential source of bias, particularly if unreported bleeds had atypically strong (or weak) associations with physical activity, as may have occurred if children failed to report bleeds perceived to have been caused by physical activity.

A bleed was defined as an episode of bleeding requiring additional clotting factor concentrate, a definition widely used by hemophilia researchers.[8] This means that subclinical bleeds were not captured. Physical activity, particularly impact loading physical activity, may produce joint damage in the absence of clinically detectable bleeds.[3] Further studies are needed to examine cumulative effects of subclinical trauma on future risk of clinically significant joint pain and disability.

A possible source of bias is that interviews were not conducted (ie, exposure data were not collected) for bleeds that occurred within 2 weeks of a preceding bleed. Such bleeds occurred most often in patients who frequently bleed. The variation in severity of bleeding phenotype among children with severe hemophilia is well recognized,[25] and it is possible that exogenous precipitants of bleeding such as physical activity may be less important in frequent bleeders. To the extent that more bleeds were excluded from frequent bleeders in whom exercise had less of an effect on bleed risk, the association between physical activity and risk of bleeding may have been overestimated.

In case-crossover studies, cases act as their own controls. Consequently case-crossover studies are not confounded by time-invariant risk factors. The main potential confounder was clotting factor level, so we adjusted for potential confounding by factor levels. Nevertheless clotting factor levels were estimated using averaged pharmacokinetic parameters. Because the relationship between the log odds of bleed and clotting factor level may not have been perfectly linear, we may have undercorrected for potential confounding.

Risk estimates were obtained for category 2 and category 3 activities. It would have been preferable to obtain separate risk estimates for every specific type of physical activity but this is not possible with achievable sample sizes.

Implications for Children With Hemophilia

This study confirms that physical activity is associated with an increased risk of bleeds in children and adolescents with moderate or severe hemophilia A or B. It demonstrates that the relative increase in risk is moderate. However, for most children, the absolute increase in risk is likely to be low.

The risk of bleeding is mitigated by prophylaxis to the extent that clotting factor levels of around 50% reduce risk of bleeds to below the risk experienced during periods of inactivity with no exogenous clotting factor (Figure 2). With typical prophylaxis regimens (doses of 35-50 IU/kg), peak factor concentrations of 70% to 100% are achieved which, given a factor VIII half-life of 10.7 hours,[11] is sufficient to maintain levels greater than 50% for between approximately 6 and 12 hours. Exposure to physical activity is quite transient (typically <12 of the 168 hours in each week[26]) and it would be expected that the increase in relative risk is also transient. In contrast, factor supplementation reduces risk for long periods yielding sustained reductions in relative risk. Consequently prophylactic clotting factor is likely to have a larger absolute effect on bleeding risk than physical activity.

In conclusion, in children and adolescents with hemophilia, vigorous physical activity was associated with an elevated risk of bleeding. Nevertheless, the absolute increase in bleeding risk associated with physical activity may be small.

Author Contributions: Dr Herbert had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Herbert, Latimer, Curtin, Monagle, Broderick.
Acquisition of data: Herbert, Latimer, Mathieu, Broderick.
Analysis and interpretation of data: Herbert, Latimer, Broderick.
Drafting of the manuscript: Herbert, Latimer, Broderick.
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