

Original Article

# Potential Role of Life Stress in Unexplained Sudden Cardiac Arrest

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## ABSTRACT

**Background:** The etiology of sudden cardiac arrest (SCA) in individuals without known cardiovascular heart disease remains elusive in nearly half of all patients after systematic testing. We investigated the relationship between stressful life events and SCA risk in cases of explained and unexplained SCA (USCA) events.

**Methods:** Individuals who previously experienced SCA were enrolled prospectively and divided into a USCA or explained SCA (ESCA) subgroup dependent on whether a diagnosis was ascribed after SCA. Participants completed either the 1997 Recent Life Changes Questionnaire, Student Stress Scale, or Social Re-adjustment Rating Scale for Non-Adults recalling events during the year preceding their SCA, depending on age at SCA presentation; all measure stress in life

## RÉSUMÉ

**Contexte :** La cause de l'arrêt cardiaque subit (ACS) chez les personnes n'ayant pas de maladie cardiovasculaire connue demeure nébuleuse dans près de la moitié des cas, même après des examens systématiques. Nous avons étudié la relation entre les événements stressants de la vie et le risque d'ACS chez des patients présentant un ACS expliqué (ACS<sub>e</sub>) ou inexpliqué (ACS<sub>i</sub>).

**Méthodologie :** Des sujets ayant déjà subi un ACS ont été recrutés de manière prospective et répartis en deux sous-groupes (ACS<sub>e</sub> et ACS<sub>i</sub>), selon qu'un diagnostic a pu ou non être posé après l'ACS. On a demandé aux participants de répondre au questionnaire RLCQ (*Recent Life Changes Questionnaire*, questionnaire sur les changements de vie récents, version de 1997), au questionnaire SSS (*Student Stress Scale*, échelle

Most sudden cardiac arrest (SCA) cases occur in older adults with underlying coronary heart disease (CHD) or structural heart disease.<sup>1,2</sup> In relatively younger adults, inherited heart rhythm disorders have been identified as important risk factors for SCA.<sup>2,3</sup> However, despite extensive evaluations, the etiology of SCA or sudden cardiac death (SCD) in those without

known coronary or structural heart disease remains elusive in nearly half of cases.<sup>2,4,5</sup>

The autonomic nervous system (ANS) is known to be a critical modulator of arrhythmogenesis in structurally normal and abnormal hearts.<sup>6,7</sup> Sympathetic activation of the ANS has been shown to modulate substrates of ventricular arrhythmias in either normal or diseased myocardium<sup>8</sup> as well as play a role in cardiovascular disease progression and risk of SCD.<sup>9</sup> Stress—a mental, physical, or emotional tension in response to various unexpected or uncertain factors and/or circumstances—induces physiological changes by shifting tone between the sympathetic and parasympathetic systems of the ANS.<sup>10</sup>

Psychosocial factors such as distress, anxiety, depression, and life dissatisfaction have been connected with increased risk for SCD and stroke.<sup>9,11,12</sup> Lane et al. investigated the role of psychological stress in idiopathic ventricular fibrillation (IVF) and reported that IVF survivors experienced moderate or severe psychological stress before their cardiac event.<sup>13</sup>

Received for publication October 7, 2020. Accepted October 28, 2020.

**Ethics Statement:** The study was approved by the UBC Children's and Women's Health Centre of British Columbia Research Ethics Board as well as the research ethics board at each participating site. Informed consent was obtained from each study participant.

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change units (LCUs). SCA group scores were compared with an age- and sex-matched control group.

**Results:** We compared 36 SCA group participants (22 USCA, 14 ESCA, age  $47 \pm 15$  years, age at SCA  $40 \pm 14$  years, 50% male) with 36 control participants (age  $47 \pm 15$  years, 50% male). There was no significant difference in LCU score between the control group and the SCA group ( $248 \pm 181$  LCU vs  $252 \pm 227$  LCU;  $P > .05$ ). The ESCA subgroup had significantly lower mean LCU scores than the USCA subgroup ( $163 \pm 183$  LCU vs  $308 \pm 237$  LCU;  $P = .030$ ).

**Conclusions:** Stressful life events, especially those producing chronic stress, might predispose otherwise healthy individuals to lethal arrhythmias. Further investigation into the role of stress in SCA precipitation is warranted.

The Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER) is a large national, multicentre registry for cases of unexplained SCA (USCA), which promotes systematic evaluation post SCA.<sup>5</sup> Within CASPER, the cause of approximately 50% of SCA cases remain elusive after rigorous examination.<sup>5</sup> The role of stressful life events (SLEs) as antecedents to SCA in individuals who had no etiology after rigorous testing has not been investigated.

The purpose of this exploratory study was to investigate whether life stress contributed significantly to SCA risk in a population of USCA victims vs those with an explained SCA (ESCA). The results of this study are intended to generate hypotheses to be tested in a larger sample of cardiac arrest survivors.

## Methods

### Recruitment

Institutional approval for this study was obtained from the UBC Children's and Women's Health Centre of British Columbia Research Ethics Board, as well as from the research ethics board at each participating site. This exploratory study was conducted within the context of a larger program of research involving cardiac arrest survivors—CASPER. Participants were identified from 3 centres already part of the CASPER network.

Children and adults older than the age of 11 years who presented with SCA were recruited for this study. Thorough systematic evaluation of SCA in participants included but was not limited to cardiac magnetic resonance imaging, signal-averaged electrocardiogram, exercise testing, drug provocation testing, electrophysiological study, and genetic testing.<sup>5</sup> SCA survivors who had no identifiable cardiac abnormalities on clinical testing and no pathogenic or likely pathogenic mutations, according to criteria by the American

d'évaluation du stress vécu par les étudiants) ou au questionnaire SRRS (*Social Readjustment Rating Scale*, échelle d'évaluation du réajustement social) pour les non-adultes en repensant aux événements survenus dans l'année précédant l'ACS, selon leur âge au moment de l'ACS; tous ces questionnaires mesurent le stress en unités de changement de vie (UCV). Les scores des patients ayant subi un ACS ont été comparés à ceux de sujets témoins appariés selon l'âge et le sexe.

**Résultats :** Nous avons comparé 36 sujets ayant subi un ACS (22 ACSi et 14 ACSe; âge :  $47 \pm 15$  ans; âge au moment de l'ACS :  $40 \pm 14$  ans; proportion d'hommes : 50 %) à 36 sujets témoins (âge :  $47 \pm 15$  ans; proportion d'hommes : 50 %). Il n'y avait pas de différence significative quant au score UCV entre le groupe témoin et le groupe ACS ( $248 \pm 181$  UCV vs  $252 \pm 227$  UCV;  $p > 0,05$ ). Les sujets du sous-groupe ACSe avaient un score UCV moyen significativement plus faible que ceux du sous-groupe ACSi ( $163 \pm 183$  UCV vs  $308 \pm 237$  UCV;  $p = 0,030$ ).

**Conclusions :** Les événements stressants, plus particulièrement ceux qui entraînent un stress chronique, peuvent prédisposer des personnes autrement en bonne santé aux arythmies mortelles. Une étude plus poussée du rôle du stress dans la survenue précipitée d'un ACS s'impose.

College of Medical Genetics and Genomics, identified on genetic evaluation were included in the USCA group. SCA survivors found to have cardiac abnormalities upon testing and/or one or more pathogenic mutations identified were included in the ESCA group. Participants who were unable to provide consent or complete the forms and questionnaires were excluded.

Recruited control group members were age- and sex-matched with those in the SCA survivors group. Control group participants were recruited through advertisement via flyers posted throughout BC Children's Hospital, the BC Children's Hospital Research Institute intranet mailing list, the Hearts in Rhythm Organization Web site, and Facebook. Those who were unable to provide consent, complete the questionnaires, had a history of SCA, or clinically relevant diagnoses were excluded.

### Evaluation of life stress

Study consent was obtained and questionnaires were administered using REDCap (Vanderbilt University, Nashville, TN) housed at the BC Children's Hospital Research Institute. We measured life stress in study participants who first experienced an SCA between ages 11 and 18 years, between ages 19 and 22 years, and at age 23 years or older, using the Social Readjustment Rating Scale (SRSS) for nonadults, Student Stress Scale (SSS), and the validated 1997 Recent Life Changes Questionnaire (RLCQ), respectively.<sup>14-16</sup> These questionnaires list a series of potentially SLEs each with an assigned, differentially weighted numerical value measured in life change units (LCUs). Evaluations were administered to age- and sex-matched control participants.

SCA survivors were asked to mark which SLEs occurred for them in the 12 months before their SCA. Similarly, control group participants answered for the same period as their sex- and age-matched participant in the SCA group. To

illustrate this, if an SCA group participant was recruited in 2018 but had their first SCA event in May of 2014, they were asked to complete the questionnaires for the year period from May 2013 to May 2014. The control group participant matched to that SCA group participant would also complete the questionnaires for the year period from May 2013 to May 2014. Aggregate scores > 500 LCUs in a 12 month period denote high recent life stress, and greater risk of illness.<sup>14</sup>

### Statistical analysis

Elevated LCU scores reported on any of the questionnaires indicated elevated life stress and readjustment. Normalcy of our data was analyzed using a Kolmogorov-Smirnov test, and mean +/- SDs calculated from each of the groups and compared using a *t* test. A *P* value < 0.05 was interpreted as significant. All analyses were conducted using SPSS for Windows Version 23 (IBM Corp, Armonk, NY).

### Results

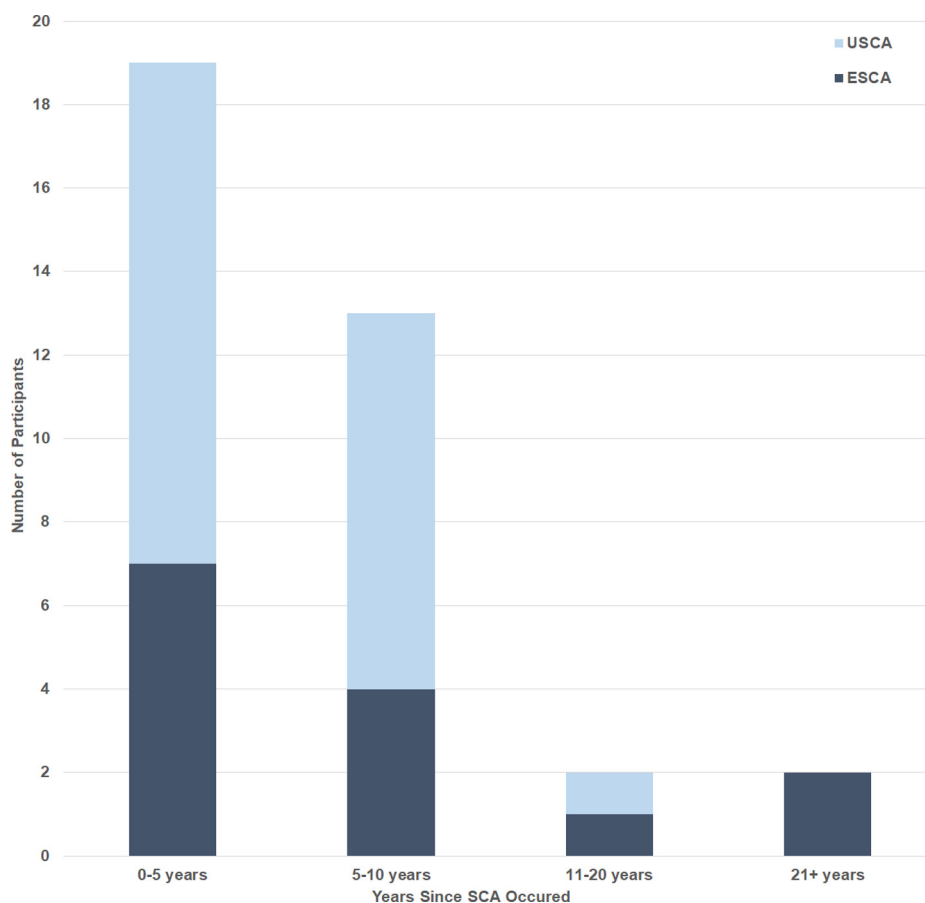
Thirty-six survivors of SCA (50% male) and 36 control participants (50% male) were recruited into the study. At time of participation, the mean age of the SCA group participants was 47 ± 15 years and control group participants was 47 ± 15 years. The mean age at the time of the SCA event in the

SCA group was 40 ± 14 years. Most patients presented with SCA within the previous 5 years (19/36; 53%; Fig. 1). The SCA participants (n = 36) were categorized into USCA (22/36; 61%) and ESCA (14/36; 39%).

### Details of circumstances of SCA

Full details and circumstantial information related to the SCA events are outlined in Table 1. The SCA events were witnessed in 33/36 (92%) of cases, and most frequently occurred in the mornings (14/36; 39%). SCA events commonly occurred at home (14/36; 39%) or in public places (14/36; 39%). At the time of, or immediately before, the SCA event, individuals were commonly at rest (12/36; 33%) or engaged in exercise (7/36; 19%). Of the 14 patients who were exercising, moderately active or vigorously active, the most common activity was jogging or running (10; 71%).

Most of the SCA events that occurred were witnessed by bystanders (33/36; 92%). Of the 36 survivors, bystanders performed onsite cardiopulmonary resuscitation in 29 (81%) cases and deployed an automated external defibrillator in 9 (25%) cases. More than half of the patients (16/29; 55%) who received bystander cardiopulmonary resuscitation showed no evidence of neurological impairment. Of the SCA survivors, 6 (17%) had transient neurological impairment, 6 (17%) had mild neurological impairment, and 5 (15%) had severe neurological impairment.



**Figure 1.** Number of years between first SCA event and participation in current study for SCA group members. ESCA, explained sudden cardiac arrest subgroup; SCA, sudden cardiac arrest; USCA, unexplained sudden cardiac arrest subgroup.

**Table 1. Demographic descriptors and circumstance of SCA group participants**

Characteristic	n	%
Unexplained SCA subgroup	22	61
Explained SCA subgroup	14	39
Sex		
Male	18	50
Female	18	50
Age at cardiac arrest, years		
11-18	2	6
19-22	2	6
≥ 23	32	89
Time of day of SCA		
Morning	14	39
Afternoon	8	22
Evening	6	17
Night	2	6
Unknown	6	17
Setting of SCA event		
Home	14	39
Public place	14	39
School	2	6
Other	5	14
Unknown	1	3
Level of activity		
Sleep	2	6
Rest	12	33
Mildly active	6	17
Moderately active	4	11
Vigorously active	3	8
Exercise	7	19
Unknown	2	6
Neurological damage from SCA		
No damage	18	50
Yes, but it went away	6	17
Yes, and it hasn't affected my life much	6	17
Yes, and it has changed my life a lot	5	14
Unknown	1	3
SCA witnessed by bystanders		
Yes	33	92
No	2	6
Unknown	1	3
CPR performed by bystander		
Yes	29	81
No	3	8
Unknown	4	11
AED used by bystander		
Yes	9	25
No	21	58
Unknown	6	17

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; SCA, sudden cardiac arrest.

## SLEs

The most common SLEs are outlined in Table 2. For the SCA survivor group, 14 (39%) experienced changes in work responsibilities, 12 (33%) experienced changes in work hours, and 11 faced a major decision about the future (31%). The control group had many overlapping SLEs. The control group respondents listed vacation most often (20; 56%), followed by change in work responsibilities (12; 33%), and change in work hours (11; 30%) whereas some reported a relationship gain (8; 22%) as stressful.

The mean aggregate LCU score of the SCA survivor group (252 ± 227) was not significantly different from the mean

**Table 2. Commonly reported stressful life events**

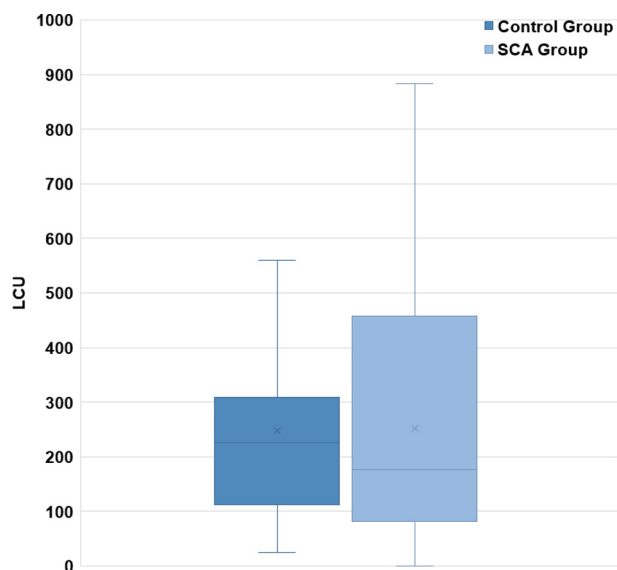
SCA group	n	%
Change in work responsibilities	14	39
Change in work hours	12	33
Major decision about future	11	31
Vacation	11	31
Control group		
Vacation	20	56
Change in work responsibilities	12	33
Change in work hours	11	31
Gain relationship	8	22

SCA, sudden cardiac arrest.

aggregate LCU score of the age- and sex-matched control group (248 ± 181;  $P > 0.05$ ; Fig. 2). Within the SCA group, the time that had passed since their cardiac arrest did not differ significantly between the 2 subgroups (USCA group: 4.5 ± 3.1 years; ESCA group: 10.1 ± 14.1 years;  $P > 0.05$ ). When we compared responses of participants within the SCA survivors group, the ESCA group had lower LCU scores compared with the USCA group (163 ± 183 LCUs vs 308 ± 237 LCUs;  $P = 0.03$ ; Fig. 3). When we compared each of the SCA subgroups with their respective age- and sex-matched control participants, LCU scores were not significantly different (USCA subgroup vs controls: 308 ± 237 LCUs vs 265 ± 205 LCUs;  $P > 0.05$ ; ESCA subgroup vs controls: 163 ± 183 LCUs vs 218 ± 134 LCUs;  $P > 0.05$ ). Similarly, there was no correlation between LCU scores and overall time from cardiac arrest ( $P > 0.05$ ) nor between LCU score vs time from cardiac arrest for each of the 2 subgroups (USCA time from SCA vs LCU score,  $P > 0.05$ ; ESCA time from SCA vs LCU score,  $P > 0.05$ ).

## Discussion

The main purpose of this exploratory study was to investigate the potential role of life stress in SCA events. Half of SCA and SCD among younger individuals remain unexplained despite extensive investigation.<sup>2,4,5</sup> Stress has been shown previously to precede cardiac events<sup>13</sup> and psychosocial factors including distress, anxiety, depression, and life dissatisfaction have been connected with increased risk for SCD and stroke.<sup>9,11,12</sup> We investigated whether SCA survivors had elevated life stress in the year before SCA. There was no significant difference between SLEs measured as LCUs between the SCA group and their age- and sex-matched control participants, which was unexpected. We expected SCA survivors to have experienced more SLEs leading up to their cardiac arrest compared with age- and sex-matched control participants because previous reports indicate that stress influences cardiac health. The result was surprising and could be because of the limitations of this study as outlined in the Limitations. The critical relationship between life stress and the heart is perhaps most effectively illustrated by Takotsubo syndrome, which is classically triggered by acute emotional stressors, such as the loss of a loved one.<sup>17</sup> A significant increase in myocardial infarction incidence is established around potentially stressful times of the year, especially Mondays, Christmas and New Year's, and spring daylight savings.<sup>18-21</sup> Temporal relationships between SCD and acutely stressful



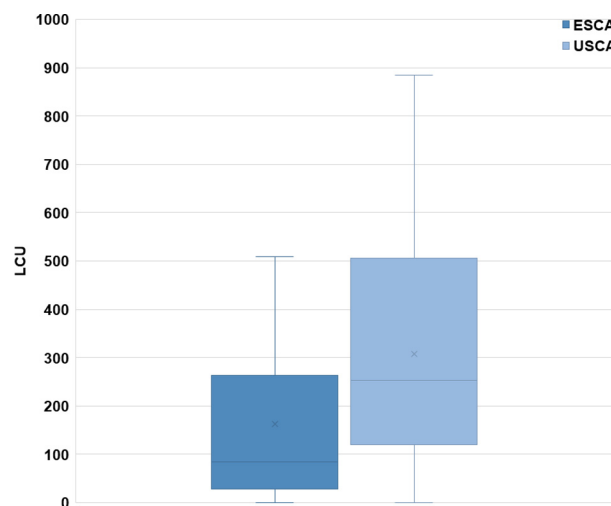
**Figure 2.** Comparison of LCU scores of the SCA and control group participants on stress inventories. The difference between the 2 groups was nonsignificant ( $P > 0.05$ ). LCU, life change units; SCA, sudden cardiac arrest.

events, such as extreme threats to personal safety or hearing of a loved one's death, have also been reported.<sup>22</sup> Phobic anxiety has been linked to CHD and SCD in men and women, and additional psychosocial factors such as distress, anxiety, depression, and life dissatisfaction have been connected with increased risk for SCD and stroke.<sup>9,11,12</sup>

The lower rates of life stress in individuals from the ESCA group compared with the USCA subgroup complemented the findings from the study by Lane et al. In their study, a significantly greater number of the IVF survivors experienced moderate or severe psychological stress before their cardiac event compared with the CHD patients.<sup>13</sup> They compared IVF survivors and CHD patients who had survived acute myocardial infarction or angina. The study by Lane et al. provided evidence for psychological stress playing a role in USCA, but reliance on participants' perceptions of the stressful events left room for memory error and bias especially without using a proper control group.

In the current study, we observed that mornings were the most common time individuals experienced SCA. This finding aligns with the robust body of literature that identify a circadian pattern of SCA incidence. A morning peak in SCA occurrence has been reported in cohort studies and prospective studies,<sup>23-26</sup> although the exact mechanisms for this circadian variation is still not well understood. However, some recent studies have noted a loss of morning peak, possibly because of the shifting sleep patterns.<sup>27</sup> Alternatively, the higher LCU scores in the USCA group could be attributed to the unexplained nature of their SCA and merits further investigation.

The connection between stress and cardiac events likely lies with the ANS. Ventricular fibrillation is a common cause of SCD, and cardiac autonomic function might be an important



**Figure 3.** Comparison of LCU scores of ESCA and USCA subgroup participants on stress inventories. The difference between the 2 groups was significant ( $P = 0.03$ ). ESCA, explained sudden cardiac arrest subgroup; LCU, life change units; USCA, unexplained sudden cardiac arrest subgroup.

factor in setting the arrhythmic threshold.<sup>28,29</sup> Psychosocial factors like stress might affect arrhythmic risk by altering the sympathetic-parasympathetic balance.<sup>30</sup> This imbalance could create an unstable cardiac state with increased risk for deadly arrhythmias, even in ostensibly healthy individuals. Although what exactly disposes individuals without an identified etiology to deadly arrhythmias is likely multifactorial; our findings suggest a role for environmental factors including chronic life stress.

### Limitations

Reliability of participants' responses on SLE checklists decreases as the recall period increases.<sup>31</sup> Although the recall period between the USCA and ESCA groups did not differ, we are limited by the accuracy of individuals' retrieval. Additionally, an individual's current state affects how they interpret past events and can distort memories, even if the memory prompt asked is considered objective.<sup>31,32</sup> Our study design attempted to limit this bias by using an objective list and scoring system for SLEs, but as already noted, even objective measures are susceptible to participants' biases. It is possible that those who lack a proper explanation for their sudden cardiac event are open to alternative explanations, such as stress, might recall stressful events more easily, might report greater stress than they were actually experiencing, or believe stressful events are worth reporting. Also, our control group might not be a true representation of the general population and perhaps were more cognizant of stress in their lives and sought participation after exposure to our advertising materials. Furthermore, because of the small sample size, we were unable to determine possible associations between other confounders such as lifestyle (exposure to illicit substances, alcohol, stimulant drinks, participation in vigorous sports, etc) and onset of SCA in this cohort.

## Conclusions

Although there were no significant differences in SLEs between the SCA group and age- and sex-matched control group, the unexplained nature of the SCA might give rise to an elevated life stress score or alternatively SLEs might predispose certain individuals to SCA, particularly those in whom a cardiac etiology is not identified. The ANS is a likely system that mediates the interaction between stress and SCA. Further, larger scale, prospective studies using more robust techniques are warranted to determine the association between potential confounders such as lifestyle for those whose SCA remains unexplained. The relationship between stress, the ANS, and other confounders such as lifestyle and SCA merits further investigation.

## Acknowledgements

The authors thank the participants for their cooperation and contribution to this study.

## Funding Sources

This study was supported by the Heart in Rhythm Organization (Dr Krahn, Principal Investigator), which receives support from the Canadian Institutes of Health Research (RN380020-406814).

## Disclosures

The authors have no conflicts of interest to disclose.

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