

# Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis

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**Background.** Individual symptoms of post-myocardial infarction (MI) depression may be differentially associated with cardiac prognosis, in which somatic/affective symptoms appear to be associated with a worse cardiovascular prognosis than cognitive/affective symptoms. These findings hold important implications for treatment but need to be replicated before conclusions regarding treatment can be drawn. We therefore examined the relationship between depressive symptom dimensions following MI and both disease severity and prospective cardiac prognosis.

**Method.** Patients ( $n=473$ ) were assessed on demographic and clinical variables and completed the Beck Depression Inventory (BDI) within the first week of hospital admission for acute MI. Depressive symptom dimensions were associated with baseline left ventricular ejection fraction (LVEF) and prospective cardiac death and/or recurrent MI. The average follow-up period was 2.8 years.

**Results.** Factor analysis revealed two symptom dimensions – somatic/affective and cognitive/affective – in the underlying structure of the BDI, identical to previous results. There were 49 events attributable to cardiac death ( $n=23$ ) or recurrent MI ( $n=26$ ). Somatic/affective ( $p=0.010$ ) but not cognitive/affective ( $p=0.153$ ) symptoms were associated with LVEF and cardiac death/recurrent MI. When controlling for the effects of previous MI and LVEF, somatic/affective symptoms remained significantly predictive of cardiac death/recurrent MI (hazard ratio 1.31, 95% confidence interval 1.02–1.69,  $p=0.038$ ). Previous MI was also an independent predictor of cardiac death/recurrent MI.

**Conclusions.** We confirmed that somatic/affective, rather than cognitive/affective, symptoms of depression are associated with MI severity and cardiovascular prognosis. Interventions to improve cardiovascular prognosis by treating depression should be targeted at somatic aspects of depression.

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**Key words:** Depression, myocardial infarction, prognosis.

## Introduction

The association of depression following myocardial infarction (MI) with progression of heart disease has been studied intensively over the last decades (Barth *et al.* 2004; Van Melle *et al.* 2004; Sørensen *et al.* 2005; Nicholson *et al.* 2006). The overall consensus is that, although some exceptions have been published, a twofold increased risk of new fatal or non-fatal cardiovascular events is observed for patients with post-MI depression (Van Melle *et al.* 2004). The extent to which this association is to be attributed to heart disease severity has been the object of debate (Lane *et al.* 2001, 2003; Carney *et al.* 2004; Van Melle *et al.* 2005;

Nicholson *et al.* 2006). Some studies have found that almost half of the variance in the association is explained away when left ventricular ejection fraction (LVEF) is added to the prediction models (Nicholson *et al.* 2006). Others have observed a dose–response-like association between LVEF at the time of MI and subsequent risk of depression (Van Melle *et al.* 2005), although quite some heterogeneity in findings is seen here as well (Carney *et al.* 2003; Lane *et al.* 2003). If the association between post-MI depression and cardiac prognosis is confounded by MI severity, this might explain the limited effects of antidepressant treatment on depression outcomes (Glassman *et al.* 2002; Berkman *et al.* 2003; Lespérance *et al.* 2007; Van Melle *et al.* 2007) and no effects at all on cardiac outcomes (Berkman *et al.* 2003; Van Melle *et al.* 2007).

Recently, it has been observed that individual symptoms of post-MI depression may be differentially

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associated with cardiovascular prognosis (De Jonge *et al.* 2006). In that study somatic/affective symptoms, including sleeping difficulties and fatigue, appeared to be associated with a worse cardiovascular prognosis than cognitive/affective symptoms including shame, guilt and negative self-image. Even though somatic/affective depressive symptoms were confounded by somatic health status, the association between somatic/affective symptoms and cardiac prognosis remained after controlling for MI severity and somatic co-morbidity. This suggests that these somatic/affective symptoms may be an important target for intervention, although this intervention may be different from interventions derived from general psychiatry. However, these findings have not yet been confirmed by other researchers. We therefore set out to replicate the findings by De Jonge *et al.* (2006), hypothesizing that only somatic/affective symptoms of depression are associated with increased cardiovascular risk in post-MI patients. In addition, we hypothesized that somatic/affective symptoms of depression are associated with baseline LVEF, but that this association does not fully explain the association with poor cardiac prognosis.

## Method

### *Study design and patient population*

Patients hospitalized for acute MI ( $n=473$ ) were recruited between May 2003 and June 2006 from four teaching hospitals (Catharina Hospital, Eindhoven; St Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; St Anna Hospital, Geldrop) in The Netherlands. Inclusion criteria were age  $>30$  years and hospitalization due to acute MI. Criteria for diagnosis of MI were troponin I levels more than twice the upper limit, with typical ischaemic symptoms (e.g. chest pain) lasting for more than 10 min or electrocardiogram (ECG) evidence of ST segment elevation or new pathological Q-waves. For patients without typical angina, the day of MI onset was identified as the day during hospitalization with peak troponin I levels  $>1.0$  and ECG evidence of ST segment elevation or new pathological Q-waves. Exclusion criteria were significant cognitive impairments (e.g. dementia) and severe medical co-morbidities that increased the likelihood of early death, such as malignant cancer, as verified by medical records and consulting the treating physician. Patients with chronic medical co-morbidities such as diabetes, renal disease, chronic obstructive pulmonary disease (COPD) and arthritis were included in the study. Depression was assessed at the time of MI and demographic and medical characteristics were obtained from the medical records. The

study protocol was approved by the institutional review boards of the participating hospitals, and after complete description of the study to the subjects, written consent was obtained from all study participants.

### *Assessment of depressive symptoms*

Within the first week of hospital admission for acute MI, patients completed the 21-item Beck Depression Inventory (BDI) (Beck *et al.* 1961). Patients were asked to respond with information about depressive symptoms for the period relating to the past week. Each item is rated on a 0–3 scale. A total score is obtained by summing together all the items. The BDI is a reliable and valid measure of depressive symptomatology (Davidson *et al.* 2006). A BDI total score  $\geq 10$  is indicative of at least mild to moderate symptoms of depression and has been associated with poor prognosis in MI patients (Frasure-Smith *et al.* 1995; Lespérance *et al.* 2002).

### *Clinical characteristics*

Clinical variables associated with post-MI prognosis were obtained from the patients' medical records. These included prior MI, LVEF, multi-vessel disease, anterior location of index MI, invasive *versus* conservative treatment of index MI, participation in rehabilitation after index MI, smoking status (self-report), body mass index (BMI), hypertension (systolic blood pressure  $>140$  mmHg, diastolic blood pressure  $>90$  mmHg), hypercholesterolaemia (total cholesterol  $>6.50$  mmol/l), systolic/diastolic blood pressure at the time of admission for index MI, history of diabetes mellitus, renal insufficiency, COPD and arthritis. The following medications prescribed to the patient at discharge were also noted:  $\beta$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, anti-coagulants, statins, diuretics, aspirin and selective serotonin reuptake inhibitors (SSRIs). Demographic variables included age, gender, marital status and classified educational level.

### *Endpoint*

The endpoint was a composite of cardiac death and/or recurrent MI, as verified by medical records. Criteria for diagnosis of MI were those used for inclusion in the study. The mean follow-up period was 2.8 years (s.d. = 1.2 years, range 6–1650 days), and follow-up data were complete for all patients (100%). There is variability in length of follow-up because the last follow-up on all patients was done at set points in time ('waves' of follow-up) while patients were enrolled

**Table 1.** Factor loadings of depressive symptom dimensions and relation to BDI items

Depressive symptoms from BDI	Dimensional structure in de Jonge <i>et al.</i> (2006)		Dimensional structure in the present study	
	Somatic/affective factor	Cognitive/affective factor	Somatic/affective factor	Cognitive/affective factor
Sadness	0.64	0.45	0.48	0.57
Pessimism	0.56	0.58	0.48	0.36
Sense of failure		0.66		0.67
Dissatisfaction	0.69	0.49	0.72	0.38
Guilt		0.70		0.71
Punishment		0.59		0.67
Self-dislike		0.72		0.69
Self-accusations		0.71		0.65
Suicidal ideas		0.49	0.35	0.52
Crying	0.52		0.39	0.32
Irritability	0.45		0.39	0.32
Social withdrawal	0.42	0.51	0.34	
Indecisiveness	0.68	0.40	0.54	0.35
Body-image change		0.57	0.42	0.32
Work difficulty	0.69		0.76	
Insomnia	0.55		0.59	
Fatigability	0.58		0.65	
Loss of appetite	0.42		0.50	
Weight loss				
Somatic preoccupation	0.67		0.51	0.42
Loss of libido	0.50		0.60	

BDI, Beck Depression Inventory.

continuously as a function of acute MI admission to hospital.

### Statistical analysis

Principal component analysis (PCA) with oblimin rotation was used to determine the underlying structure of the BDI. A scree plot was adopted to identify the number of components, and subsequent Kaiser–Meyer–Olkin (KMO) testing and Bartlett’s test of sphericity were applied as fit indices. Discrete variables were compared with the  $\chi^2$  test and are presented as numbers and percentages. Continuous variables were compared with the Student’s *t* test and are presented as mean values and standard deviations. Linear regression analyses were used to evaluate the relationship between depression and LVEF. Cox proportional hazard regression analyses were performed to investigate the impact of depression on cardiovascular events at follow-up. For all tests to indicate statistical significance  $p < 0.05$  was used. Hazard ratios (HR) with 95% confidence intervals are reported. All statistical analyses were performed using SPSS version 14.0 for Windows (SPSS Inc., USA).

## Results

### Factor structure

PCA revealed a two-component solution in the underlying structure of the BDI (Table 1). The KMO test (0.87) and Bartlett’s test of sphericity ( $p < 0.001$ ) indicated that PCA was adequate for these data. The total variance explained was 35%. The two factors that were constructed from the PCA reflect somatic/affective and cognitive/affective symptoms of depression. The labelling of the components was based on de Jonge *et al.* (2006).

### Demographic and clinical characteristics

Of the original 473 patients, 54 had no echocardiography, leaving 419 (89%) patients to be included in further analyses. Table 2 shows demographic and clinical characteristics of the current sample. Of the 419 MI patients, 22% were female, 16% had had a previous MI, 14% were known to have diabetes mellitus, 61% were invasively treated for index MI and 62% received cardiac rehabilitation. Mean age was 59 years and mean BMI was 27 kg/m<sup>2</sup>. Patients

**Table 2.** Demographic and clinical baseline predictors of death or recurrent MI (univariate analyses)

	All patients (n=419)	Death or MI (n=49)	Event-free (n=370)	HR	95% CI	p
<b>Demographic characteristics</b>						
Age, years				1.04	1.01–1.07	0.003
Mean (s.d.)	59 (11)	64 (13)	59 (11)			
Female gender	91 (22)	7 (14)	84 (23)	0.60	0.27–1.34	0.216
Partner	344 (82)	38 (78)	306 (83)	0.78	0.39–1.56	0.476
Educational level: high	237 (57)	22 (45)	215 (58)	0.67	0.38–1.18	0.169
<b>Clinical characteristics</b>						
Disease severity						
Previous MI	65 (16)	19 (39)	46 (12)	3.86	2.12–7.01	<0.001
LVEF (%)				0.97	0.94–0.99	0.007
Mean (s.d.)	51 (12)	47 (14)	52 (12)			
Multi-vessel disease	136 (32)	17 (35)	119 (32)	1.28	0.68–2.42	0.440
Anterior MI location	159 (38)	19 (39)	140 (38)	1.16	0.63–2.13	0.636
Co-morbidity						
Diabetes mellitus	59 (14)	9 (18)	50 (14)	1.36	0.66–2.81	0.400
Renal insufficiency	19 (5)	4 (8)	15 (4)	2.00	0.72–5.56	0.184
COPD	31 (7)	5 (10)	26 (7)	1.40	0.56–3.54	0.473
Arthritis	32 (8)	6 (12)	26 (7)	1.80	0.77–4.23	0.178
Invasive treatment <sup>a</sup>	255 (61)	20 (41)	235 (64)	0.43	0.24–0.75	0.003
Cardiac rehabilitation	260 (62)	26 (53)	234 (63)	0.62	0.35–1.11	0.107
Medication use						
$\beta$ -Blockers	363 (87)	40 (82)	323 (87)	0.65	0.32–1.35	0.250
ACE inhibitors	160 (38)	20 (41)	140 (38)	1.08	0.61–1.92	0.782
Anti-coagulants	347 (83)	44 (90)	303 (82)	1.92	0.76–4.84	0.167
Statins	381 (91)	40 (82)	341 (92)	0.40	0.20–0.83	0.014
Aspirin	344 (82)	34 (69)	310 (84)	0.45	0.25–0.83	0.010
Diuretics	80 (19)	21 (43)	59 (16)	3.55	2.01–6.25	<0.001
SSRIs	53 (13)	10 (20)	43 (12)	1.79	0.89–3.58	0.101
Smoking	164 (39)	22 (45)	142 (38)	1.25	0.71–2.20	0.435
BMI (kg/m <sup>2</sup> )				0.91	0.84–0.99	0.032
Mean (s.d.)	27 (4)	26 (5)	27 (4)			
Hypertension	116 (28)	12 (24)	104 (28)	0.75	0.39–1.45	0.394
Hypercholesterolaemia	50 (12)	3 (6)	47 (13)	0.48	0.15–1.54	0.214
<b>Cardiac function</b>						
Systolic BP (mmHg)						
Mean (s.d.)	140 (29)	136 (24)	141 (29)	0.99	0.98–1.00	0.207
Diastolic BP (mmHg)						
Mean (s.d.)	82 (17)	80 (17)	82 (17)	0.99	0.97–1.01	0.204

MI, Myocardial infarction; HR, hazard ratio; CI, confidence interval; s.d., standard deviation; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; SSRI, selective serotonin reuptake inhibitor; BMI, body mass Index; BP, blood pressure.

Values are given as n (%) patients unless otherwise indicated.

<sup>a</sup> Percutaneous coronary intervention or coronary artery bypass graft surgery.

used the following medication:  $\beta$ -blockers (87%), ACE inhibitors (38%), anti-coagulants (83%), statins (91%), aspirin (82%) and SSRIs (13%). Only 19% were on diuretics. Of patients, 39% smoked, 28% had hypertension and 12% hypercholesterolaemia. The mean LVEF was 51%.

#### Association with LVEF

In univariate regression analyses, somatic/affective ( $\beta = -0.099$ ,  $t = -2.03$ ,  $p = 0.043$ ) but not cognitive/affective symptoms ( $\beta = -0.017$ ,  $t = -0.34$ ,  $p = 0.733$ ) were related to LVEF. Entering both symptom

dimensions simultaneously into the model confirmed that increased somatic/affective ( $\beta = -0.110$ ,  $t = -2.07$ ,  $p = 0.039$ ) but not cognitive/affective symptoms ( $\beta = 0.028$ ,  $t = 5.30$ ,  $p = 0.596$ ) were related to decreased LVEF.

#### Clinical predictors of death or recurrent MI

There were 49 events attributable to cardiac death ( $n = 23$ ) or recurrent MI ( $n = 26$ ). In univariate analyses, patients experiencing a clinical event were older ( $p = 0.003$ ), more likely to have had a previous MI ( $p < 0.001$ ), to be treated with diuretics ( $p < 0.001$ ) and to have lower mean LVEF ( $p = 0.007$ ) and BMI ( $p = 0.032$ ) than event-free patients (Table 2). These patients were also less likely to have had invasive treatment during hospitalization for the index MI ( $p = 0.003$ ), and to be treated with statins ( $p = 0.014$ ) and aspirin ( $p = 0.010$ ), than event-free patients. When entering all these potential confounders into a multivariate analysis, only previous MI remained as an independent predictor. Hence, we adjusted for previous MI – in addition to LVEF – in subsequent multivariate analyses.

#### Depressive symptoms and prognosis

Relating depressive symptoms with time-related cardiac death or recurrent MI resulted in significant associations for somatic/affective ( $p = 0.010$ ) but not cognitive/affective symptoms ( $p = 0.153$ ) (Table 3, model 1). The association of the somatic/affective factor with cardiac death or recurrent MI remained statistically significant when the two depression factors entered the Cox regression model simultaneously ( $p = 0.030$ ) (Table 3, model 2). When controlling for the effects of previous MI and LVEF, somatic/affective symptoms remained significantly predictive of cardiac death or recurrent MI ( $p = 0.038$ ). In this analysis, previous MI was also an independent predictor of death or recurrent MI ( $p < 0.001$ ) (Table 3, model 3).

Survival curves for the two groups (somatic/affective, cognitive/affective) based on the 20% highest scoring individuals are presented in Fig. 1. The corresponding log-rank tests to assess the significance of the relationships were 3.69 for the somatic/affective ( $p = 0.055$ ) and 1.49 for the cognitive/affective symptoms ( $p = 0.221$ ).

#### Discussion

In a sample of 473 MI patients we replicated findings presented earlier by De Jonge *et al.* (2006): (1) the dimensional structure of depressive symptoms following MI was strikingly comparable; (2) only somatic/affective depressive symptoms were associated with

**Table 3.** Predictors of death or recurrent MI<sup>a</sup>

Predictor variables	Death or MI ( $n = 49$ )	
	HR (95% CI)	$p$
Model 1 <sup>b</sup>		
Somatic/affective symptoms	1.39 (1.08–1.79)	0.010
Cognitive/affective symptoms	1.17 (0.94–1.44)	0.153
Model 2 <sup>c</sup>		
Somatic/affective symptoms	1.37 (1.03–1.82)	0.030
Cognitive/affective symptoms	1.03 0.81–1.32	0.797
Model 3 <sup>c</sup>		
Somatic/affective symptoms	1.31 (1.02–1.69)	0.038
Previous MI	3.25 (1.75–6.03)	<0.001
LVEF	1.50 (0.81–2.79)	0.201

MI, Myocardial infarction; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction (<40%).

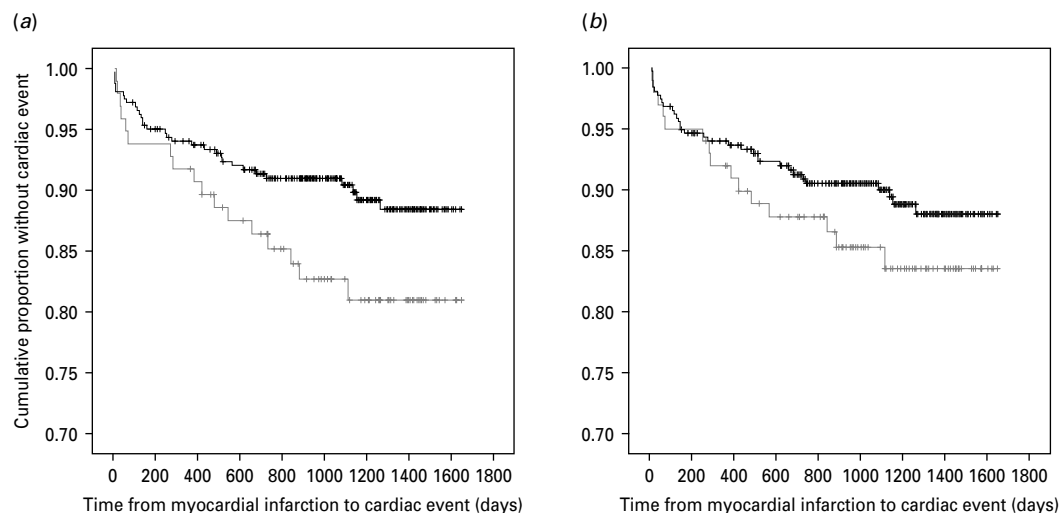
<sup>a</sup> Enter procedure.

<sup>b</sup> Univariate analyses.

<sup>c</sup> Multivariate analyses.

baseline LVEF; (3) somatic/affective depressive symptoms were associated with adverse cardiac prognosis; (4) the associations remained after controlling for confounders including LVEF. The need to replicate new findings cannot be overstated given the risk of chance capitalization. The fact that the present findings were consistent with those of De Jonge *et al.* (2006) certainly strengthens the position that depressive symptoms following MI are differentially related to cardiovascular prognosis.

There is considerable evidence that depression is a risk factor for adverse cardiovascular events in cardiac patients. However, a frequent criticism of this literature is that the association between depression and adverse prognosis may be confounded by worse baseline cardiac disease severity in depressed patients. A recent study (Lett *et al.* 2008) in patients with stable coronary heart disease found little evidence that depression is associated with worse cardiac disease severity, while the present findings clearly indicate that in acute MI patients somatic/affective depressive symptoms are associated with MI severity. Even though somatic/affective depressive symptoms were confounded by disease severity, they were still prospectively associated with medical outcome. These findings confirm previous studies indicating that somatic depressive symptoms are associated with disease severity (Watkins *et al.* 2003; De Jonge *et al.* 2006), but also that somatic/affective symptoms have an independent effect on adverse cardiac outcome while cognitive/affective symptoms have not.



**Fig. 1.** Event-free survival time following myocardial infarction and relationship with depressive symptoms ( $n=419$ ). (a) Somatic/affective symptoms; (b) cognitive/affective symptoms.

In the Heart and Soul study it was concluded that somatic depressive symptoms were associated with lower heart rate variability, while cognitive depressive symptoms were not (De Jonge *et al.* 2007b). This can be a potential mechanism underlying the relation between depression and cardiovascular prognosis. Moreover, several of the potential mechanisms that may account for the cardiac effects of depression may be reversed, e.g. increased cytokine levels resulting from left ventricular dysfunction and social and physical limitations that arise from disease itself may play a role in the genesis of post-MI depression (De Jonge *et al.* 2007a). Possibly, in some patients worse MI severity may trigger somatic depressive symptoms and, subsequently, the confluence of MI severity and somatic depressive symptoms leads to adverse medical outcome. This would imply that interventions to improve cardiovascular prognosis by treating depression should be specifically aimed at somatic aspects of depression. Exercise could be an important avenue in that matter (Barbour *et al.* 2007).

In response to previous findings by De Jonge *et al.* (2006) on the differential association between depressive symptom dimensions and cardiovascular prognosis, Thombs *et al.* suggested that results could be explained by multicollinearity, as the two dimensions were highly correlated (Thombs *et al.* 2006). Although we feel this possibility was effectively ruled out, the current results further suggest that those previous findings were quite stable. In the present study, the HR of the somatic/affective symptom dimension regarding cardiovascular events was 1.39 in the univariate model, which persisted when the cognitive/affective dimension was added (HR 1.37).

We therefore conclude that multicollinearity does not explain the current findings.

In this study the BDI was used to assess depressive symptoms. It would be of interest to replicate this work using other instruments, particularly those with proportionately more somatic items such as the Hamilton Rating Scale for Depression (Hamilton, 1960). With reference to this issue, a recent study that used the nine-item Patient Health Questionnaire (Kroenke *et al.* 2001) to assess depression severity in post-MI patients indicated that somatic symptoms of depression are often overlooked in these patients (Smolderen *et al.* 2009), while these symptoms may have substantial prognostic power in the prediction of adverse clinical events post-MI. Further, this distinction between somatic and cognitive symptoms of depression may equally be of importance in other cardiac conditions such as chronic heart failure (Schiffer *et al.* in press).

Some limitations of the current study should be noted. First, the low number of women (22%) limits the generalizability of the results. Furthermore, patients were relatively healthy with a mean LVEF of 51%. Third, somatic depressive symptoms in MI patients can be confounded by complaints originating from cardiovascular disease itself. We tried to resolve this issue by evaluating a broad spectrum of possible confounding factors, including disease severity, medical co-morbidity, risk factors and medication use. Finally, we had no information on the overall response rate of the study. However, we were able to look into a subsample of patients ( $n=63$ ). Of the 63 patients who met the inclusion criteria, 46 patients gave informed consent, leaving a response rate of 73%. The retention rate of this study has been reported. Despite these

limitations, this study was a multi-centre study, making generalization of our results to MI patients more justified.

In summary, we confirmed previous findings (De Jonge *et al.* 2006) that somatic/affective, rather than cognitive/affective symptoms of depression are associated with MI severity and cardiovascular prognosis. The results from this study indicate the need for future research directed to the identification of specific depressive symptoms that are most toxic in terms of predicting adverse cardiovascular prognosis, and to the testing of interventions to alleviate the associated risk.

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### Declaration of Interest

None.

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