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Does moderate to vigorous physical activity mediate the association between depression and physical function in midlife: Evidence from two British birth cohort studies

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ABSTRACT

Background: Mental health and physical health are intrinsically linked, yet the mechanisms are not well understood. We investigated whether moderate-vigorous physical activity (MVPA) mediated the association between depression and physical function (PF) in midlife.

Methods: Individuals from two UK birth cohorts born within one week in 1958 ($n = 7278$) and 1970 ($n = 6097$) with data on depression (ages 33/34; Malaise Inventory), MVPA (age 42; self-reported) and PF (ages 50/56; Short Form-36 subscale). Covariates included sex, childhood and adulthood social class, maternal mental health, childhood mood, alcohol consumption, smoking habits, sleep, marital status, BMI and long-standing illness/disability. Linear or multinomial logistic regression models examined associations between depression, MVPA and PF. We used a parametric g-computation mediation analysis approach to estimate percent differences in PF.

Results: Depression was associated with less frequent MVPA and poorer PF. Lower MVPA was associated with worse PF. The direct effect – randomised analogue not operating via MVPA – of depression on PF was −18.8 % (95%CI:–25.8,-11.8) and −15.8 % (20.6,-11.0) in the 1958 and 1970 cohorts, respectively. The indirect effect – operating via MVPA – was −0.5 % (−1.0,-0.03) and −0.2 % (−0.6, 0.3), resulting in a total proportion mediated of 3.1 % (0.1, 6.0) and 0.9 % (−1.6, 3.4).

Limitations: MVPA was self-reported. Intermediate confounders and mediators were measured at the same age, however associations did not change in sensitivity analysis considering age 46 MVPA (1958 cohort).

Conclusions: Although higher MVPA was protective against poor PF, there was only minor evidence that it mediated the association between depression and PF. Further investigation into other potential mediators of pathways from mental to physical health is needed.

1. Introduction

The co-dependence of mental and physical health is well recognised. Individuals with mental illness have a higher prevalence of physical disorders, including musculoskeletal, respiratory, cardiovascular, metabolic and infectious diseases (De Hert, Correll, Bobes, et al., 2011). Excess mortality is two to three times higher in those with severe mental illness than the general population, representing a 13 to 30 year shortened life expectancy (De Hert et al., 2011; Harris & Barraclough, 1998; Laursen, Munk-Olsen, Nordentoft, & Mortensen, 2007; Roshanaei-Moghaddam & Katon, 2009; Tidemalm, Waern, Stefansson, Elofsson, & Runeson, 2008); this excess mortality is largely attributable to the higher prevalence of poor physical health or illness (De Hert et al., 2011; Hoang, Goldacre, & Stewart, 2013; Saha, Chant, & McGrath, 2007). However, the mechanisms through which mental health contributes to physical health are not well understood.

One potential mediator may be moderate to vigorous physical activity (MVPA). Global meta-analyses have demonstrated that individuals with mental illness are considerably more sedentary and take part in less MVPA than healthy controls (Schuch, Vancampfort, Firth, et al., 2017;

Abbreviations: BCS70, 1970 British Cohort Study; BMI, body mass index; MVPA, moderate-vigorous physical activity; NCDS58, 1958 National Child Development Study; PA, physical activity; PF, physical function; rNDE, randomised interventional analogue of the natural direct effect; rNIE, randomised interventional analogue of the natural indirect effect; RR, relative risk ratios; SD, standard deviation; SF-36, Short-Form 36; TCE, total causal effect.

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Vancampfort, Firth, Schuch, et al., 2016; Vancampfort, Firth, Schuch, et al., 2017). Lower engagement in MVPA could be a consequence of somatosensory symptoms, low mood, fatigue, higher perceived stress or low social support (Firth et al., 2016). Low MVPA may subsequently impact physical function via decreased muscular strength, poor balance and mobility, and lower cardiorespiratory fitness (Ferreira, Sherrington, Smith, et al., 2012). Physical activity (PA) has been postulated as a restorative process between positive mental health and wellbeing and other physical health outcomes, while inactivity may deteriorate the processes that mediate this relationship (Boehm & Kubzansky, 2012).

However, investigation of PA as a mediator between mental health and physical function outcomes is rare. Data from the English Longitudinal Study of Ageing (aged 50+ at baseline) suggests that both social interaction (proportion mediated: 1.3 %) and PA intensity (7.5 %) mediate the association between mental health and subsequent physical function (Ohrnberger, Fichera, & Sutton, 2017). This has important implications, given the recent shift towards physical and social prescribing and the development of policy guidelines on health behaviours as alternative treatments for mental illness (Firth, Solmi, Wootton, et al., 2020; Schuch et al., 2016; World Health Organisation, 2004). However, frequency, time and type of activity was not specified, and the study sample consisted of older adults, who may already have poor physical function at baseline. As government guidelines on PA participation develop and prescription of lifestyle behaviours to improve health continues to rise (Bull, Al-Ansari, Biddle, et al., 2020; Sarris, O'Neil, Coulson, Schweitzer, & Berk, 2014), it is crucial to understand what aspect of PA mediates this association and if this association extends to young and middle-aged adults. The aim of this study was to investigate how MVPA mediated the association between depression and physical function in early midlife in two age-homogenous, population-representative birth cohorts.

2. Materials and methods

2.1. Sample

The 1958 National Child Development Study (NCDS58) and the 1970 British Cohort Study (BCS70) are ongoing British birth cohorts of individuals born within one week of another in England, Scotland and Wales. Both samples have been described in extensive detail elsewhere (Elliott & Shepherd, 2006; Power & Elliott, 2006). Briefly, NCDS58 included 17,415 individuals at birth, with data collected at 11 different waves from birth until age 55. BCS70 included 17,196 individuals at birth with data collection at nine waves from birth until age 46. Both cohorts were augmented with a further 920 and 400 individuals who immigrated during childhood. Individuals were eligible for inclusion in analyses if they had data on depression (NCDS58: age 33; BCS70: age 34), MVPA (NCDS58: age 46; BCS70: age 42) and physical function (NCDS58: age 50; BCS70: age 46). See Fig. 1 for derivation of analytical sample sizes (Centre for Longitudinal Studies, 2021; Johnson & Brown, 2015). Informed consent was obtained from participants at all waves. Ethical approval for the most recent waves was given for NCDS58 by the London multi-centre Research Ethics Committee and for BCS70 by National Research Ethics Service Committee South East Coast–Brighton and Sussex.

2.2. Depression (exposure)

Depressive symptoms were measured using a modified version of the Malaise Inventory (Rodgers, Pickles, Power, Collishaw, & Maughan, 1999). Based on the original 24-item inventory, it includes the 9 items with the highest loadings for the first principal factor from analyses of previous sweeps of NCDS58 and BCS70 and is commonly used in multipurpose questionnaires (Ploubidis & Cogo-Moreira, 2019; Johnson, 2015). At age 33, NCDS58 participants self-completed the inventory on a paper scale. At age 34, BCS70 cohort members used computer-assisted-self-interviewing. Individuals who gave an affirmative response on 4 or

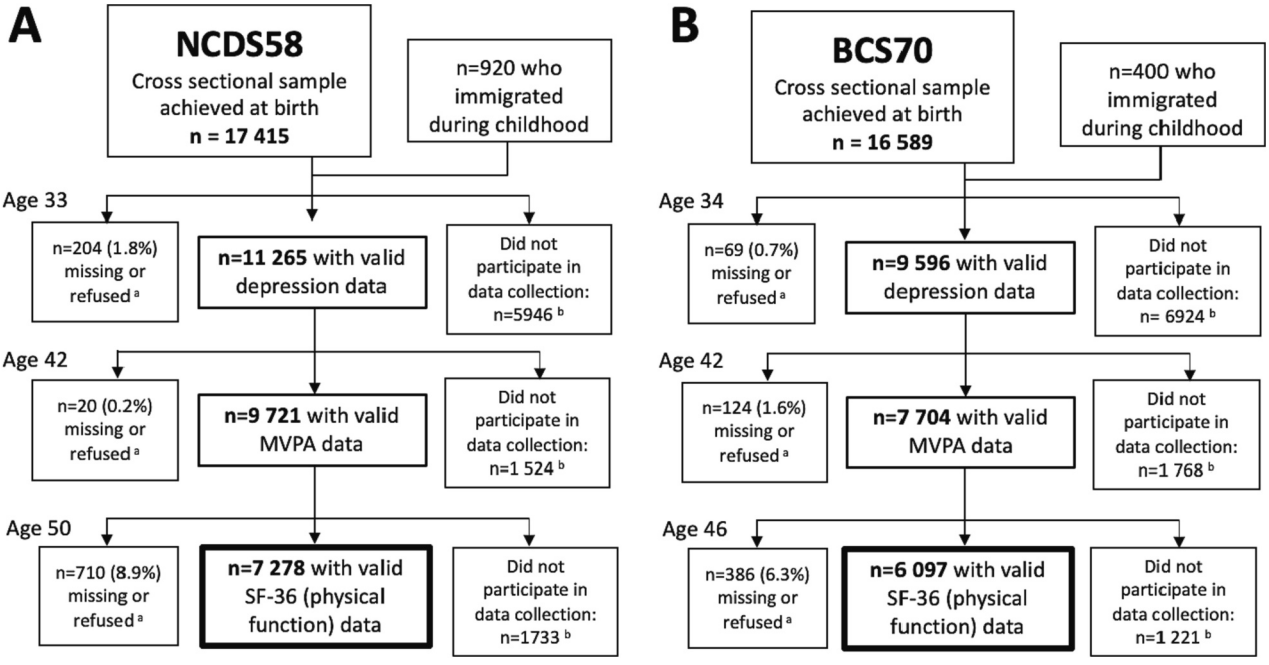

Fig. 1. Derivation of study sample for the A. 1958 National Child Development Study (NCDS58) and B. 1970 British Cohort Study (BCS70).
[a] Proportion of sample who did not have valid data on the exposure, mediator or outcome of interest, despite participating in the data collection wave at each given wave.
[b] Non-participation numbers are a subset of the sample of interest specific to this research question. Full details on loss to follow-up at all waves including reason for non-participation (death, emigration, refusal, unable to trace, etc.) has been documented elsewhere (Centre for Longitudinal Studies, 2021; Johnson & Brown, 2015).

Table 1
Sample characteristics of BCS70 and NCDS58 participants included in analysis expressed as n(%) unless specified.

		NCDS58 (n = 7278)		BCS70 (n = 6097)
EXPOSURE: Depression *(ages 33/34)*		464 (6.4)		846 (13.9)
MEDIATOR: MVPA *(age 42)*				
<1 day/ week		4072 (56.0)		1658 (27.2)
1 day/ week		910 (12.5)		742 (12.2)
2–3 days/ week		1192 (16.4)		1836 (30.1)
4–5 days/ week		460 (6.3)		1056 (17.3)
6–7 days/ week		644 (8.9)		805 (13.2)
OUTCOME: Physical function score *(age 50/46)*				
Median (Quartile 1, Quartile 3)		95 (85, 100)		95 (85, 100)
Mean ± SD		86.7 ± 21.0		86.9 ± 22.6
BASELINE COVARIATES				
Sex Female		3869 (53.2)		3268 (53.6)
Poor familial mental health[a,b] ***(ages 7,10)***		146 (2.5)		111 (2.2)
Low childhood mood[a,c] ***(ages 11, 10)***				
Doesn't apply		2339 (37.3)		326 (6.1)
Applies somewhat		3729 (60.0)		4756 (88.7)
Certainly applies		200 (3.2)		283 (5.3)
Father's social class [a] ***(ages 11, 10)***				
I Professional, II Managerial/technical		1660 (26.8)		1796 (33.8)
III Skilled non-manual or manual		3204 (51.8)		2620 (49.3)
IV Partly skilled, V Unskilled		1323 (21.4)		898 (16.9)
Smoking habits *(ages 23, 26)*				
Never smoker		2074 (32.4)		2312 (49.6)
Ex-smoker		2000 (31.2)		738 (15.8)
Current smoker		2336 (36.4)		1611 (34.6)
Alcohol consumption *(ages 23, 26)*				
Most days		1300 (20.2)		1328 (28.6)
1-2×/week		3126 (48.6)		1755 (37.7)
Less often		849 (13.2)		1065 (22.9)
Special occasions		904 (14.1)		354 (7.6)
Never		250 (3.9)		148 (3.2)
MVPA *(ages 23, 29)*	None in last month	3240 (50.4)	<1 day/ week	2689 (46.5)
	1–3 days/month	1093 (17.0)	1 day/ week	812 (14.0)
	1–2 days/week	228 (19.1)	2–3 days/ week	1260 (21.8)
	3–4 days/week	482 (7.5)	4–5 days/ week	499 (8.6)
	5+ days/week	384 (6.0)	6–7 days/ week	528 (9.1)
Long-standing illness or disability *(ages 23, 29)*		242 (3.8)[e]		1300 (22.5)[d]
INTERMEDIATE COVARIATES *(all age 42)*				
Own social class[a]				
I Professional, II Managerial/technical		2857 (45.1)		2847 (53.10)
III Skilled non-manual or manual		2581 (40.7)		1827 (34.1)
IV Partly skilled, V Unskilled		904 (14.3)		688 (12.8)
Smoking status				
Never smoker		3454 (47.5)		3010 (49.4)
Ex-smoker		1915 (26.3)		1787 (29.3)
Current smoker		1908 (26.2)		1299 (21.3)
Alcohol consumption				
Most days		1447 (19.9)	4+ x/week	932 (16.8)
2–3 days/week		2427 (33.4)	2-3×/week	1770 (31.9)
2–4 x/month		2189 (30.1)	2–4 x/month	1318 (23.8)
Special occasions		866 (12.2)	Monthly or less	1064 (19.2)
Never		329 (4.5)	Never	465 (8.4)
Marital status				
Single and never married		554 (7.6)		1332 (21.9)
Married or civil partner		5999 (82.7)		4026 (66.1)
Divorced, widowed, separated		702 (9.7)		734 (12.1)
Long-standing illness or disability		2062 (28.3)[d]		1648 (27.2)[f]
Difficulty falling or staying asleep		1485 (20.5)[h]		1146 (20.6)[g]
BMI (kg/m^2), mean ± SD		25.8 ± 4.5		26.7 ± 5.2

[a] Harmonised based on guides from CLOSER available from UK Data Service.
[b] NCDS58: Home health visitor assessed without questioning the family whether the family were experiencing difficulties due to mental illness or neurosis. BCS70: Dichotomised at 97th percentile on maternal 24-item Malaise scale for comparability with prevalence of families with poor mental health at age 7 in NCDS58 (3 %).
[c] NCDS58: Parent reported if child "is miserable or tearful". BCS70: Parent reported if child "often appears miserable, unhappy, tearful or distressed".
[d] NCDS58 & BCS70: Participants were asked if they "[had] any long-standing illness, disability or infirmity?"
[e] NCDS58: Participants were asked if they "[had] a long-standing illness/disability which limits [their] activities in any way compared with people of [their] own age]".
[f] BCS70: Participants were asked if they "[had] any Do you have any physical or mental health conditions or illnesses lasting or expected to last 12 months or more?
[g] BCS70: Responded 'All of the time', 'Most of the time' or 'A good bit of the time' when asked about the frequency of waking and having trouble falling back asleep in the last 4 weeks.
[h] NCDS58: Responded 'Yes' when asked if they normally had difficulty falling or staying asleep.

more items were considered to have elevated depressive symptoms (Ploubidis & Cogo-Moreira, 2019; Johnson, 2015), referred henceforth as depression.

2.3. Moderate to vigorous physical activity (MVPA; mediator)

At age 42, BCS70 cohort members were asked how many days in a typical week they exercised ≥30 min where they were working hard enough to raise their heart rate and break into a sweat (responses: 0–7). At age 42, NCDS58 cohort members were asked if, and how often, they regularly take part in exercise (responses: less often, 2-3× month, 1× week, 2-3× week, 4-5× week, daily), and if they get out of breath or sweaty (responses: most times, sometimes, rarely, never). For consistency across cohorts, responses were recoded as: <1 week, 1 day/week, 2–3 days/week, 4–5 days/week and 6–7 days/week. NCDS58 individuals who responded rarely or never to being out of breath or sweaty were scored as <1 week.

2.4. Physical function (outcome)

Physical function was assessed at age 46 in BCS70 and age 50 in NCDS58 using the 10-item physical function component of the Short-Form 36 (SF-36; Saris-Baglama, Dewey, Chisholm, et al., 2010). Items measured how respondents' health impacted their ability to do different activities such as lifting or carry groceries or walking more than a mile using a three-point scale ('Yes, limited a lot'; 'Yes, limited a little'; 'No, not limited at all'). Scores were summed and transformed to a 100-point scale, with lower scores indicating greater physical limitations (Saris-Baglama et al., 2010). See Supplementary Table 1 for individual item description and prevalence.

2.5. Confounders

Baseline and intermediate confounding variables were identified a priori based on established associations with the exposure, mediator and outcome. Baseline confounders included sex, father's social class (NCDS58: age 11, BCS70: age 10), maternal mental health (NCDS58: age 7, BCS70: age 10), childhood mood (NCDS58: age 11, BCS70: age 10), alcohol consumption (NCDS58: age 23, BCS70: age 26), smoking habits (NCDS58: age 23, BCS70: age 26), prior MVPA (NCDS58: age 23, BCS70: age 29) and long-standing illness/disability (NCDS58: age 23, BCS70: age 29). Intermediate confounders, all assessed at age 42 in both cohorts, included own social class, alcohol consumption, smoking habits, marital status, body mass index (BMI), sleep and long-standing illness/disability. Details of ascertainment and modelling of confounders are described in Table 1 and Supplementary Tables 2 and 3. An overview of data collection timepoints is provided in Fig. 2A, with a simplified directed acyclic graph outlining hypothesised pathways between confounders, exposure, mediator, and outcome in Fig. 2B.

2.6. Statistical analyses

Due to differences in temporality and operationalisation of variables, BCS70 and NCDS58 cohorts were analysed separately. Characteristics of the exposure, mediator, outcome and covariates are described using means (standard deviation(SD)) or sample size (%). Initial models examined associations between the exposure, mediator and outcome. Sex-interactions were assessed, and where significant, models were stratified by sex. Linear regressions modelled associations between: i) depression (*exposure*) and physical function (*outcome*) and ii) MVPA (*mediator*) and physical function (*outcome*). Multinomial logistic regressions modelled associations between iii) depression (*exposure*) and MVPA (*mediator*). For each, a sex-adjusted (or sex-stratified) model is presented, followed by a second model adjusting for all baseline covariates; intermediate covariates were not included in the model to avoid overadjustment bias (van Zwieten et al., 2022). Due to a heavy left skew, physical function scores were log-transformed (1.1 points added to all scores to avoid logarithmic values of 0 or 1) and multiplied by 100 %, allowing regression coefficients to be interpreted as symmetrical percent differences (Cole & Kryakin, 2000). Missing covariate data ranged from 0.02 % for smoking (age 42) to 23.7 % for alcohol consumption(age 26) in BCS70 and from 0.3 % for marital status (age 42) to 18.1 % for childhood familial mental health in NCDS58. Multiple imputation by chained equations was used to impute missing covariate data, with estimates from 25 imputed datasets combined using Rubin's rules (Rubin, 2004); all variables described above were included in the imputation model (exposure, mediator, outcome, covariates).

2.7. Mediation analysis

We used parametric G-computation using Monte Carlo simulations, a mediation approach that defines analogues of the indirect and direct effects using counterfactual scenarios (*gformula* command in Stata (Daniel, De Stavola, & Cousens, 2011)). Briefly, this approach partitions the total causal effect (TCE) of depression on physical function into randomised interventional analogues of the natural indirect effect (rNIE), operating via the MVPA mediator, and the natural direct effect (rNDE), not operating via MVPA (Daniel et al., 2011; VanderWeele & Tchetgen Tchetgen, 2017).The ***TCE*** is derived by comparing two hypothetical scenarios, one where the whole sample has depression and one where the whole sample does not have. The ***rNDE*** is also derived by comparing these two hypothetical situations, however in both scenarios, the distribution of MVPA is changed to the distribution it would take if the sample did not have depression. As MVPA is the same in both scenarios, any pathway from depression to MVPA is therefore eliminated, allowing the direct effect of depression on physical function, to be modelled. Finally, the ***rNIE*** is defined as the difference between the TCE and rNDE, and allows the total randomised analogue of the proportion mediated to be calculated. Note the direct and indirect effects cannot be directly estimated given that intermediate confounders are affected by the exposure, however the analogues of these effects, based on less stringent assumptions and randomised interventions, indicate realistic scenarios that could arise as a result of interventions presented in the hypothetical situations above (VanderWeele & Tchetgen Tchetgen, 2017). Estimates are expressed as percent differences in physical function and confidence intervals are obtained using a bootstrap approach with 1000 iterations. Detailed explanation of this analytical approach including adapted code has been previously published (Daniel et al., 2011).

2.8. Sensitivity analysis

We conducted two main sensitivity analyses. To enable comparable harmonisation of the exposure, mediator and outcome between cohorts and restricted by the temporality of data collection, intermediate confounders and the mediator were assessed at the same age (42 years). Therefore, to assess the impact of overlapping temporality at age 42, we replicated analysis in NCDS58 using MVPA at age 46 as a mediator so that the measurement of intermediate confounders preceded measurement of the mediator. For the second sensitivity analysis, we used two binary variables to assess if associations between depression and physical function were driven by high (6–7 days/week vs ≤5 days/week) or low (<1 day/week vs ≥1 days/week) MVPA frequency. Additionally, the impact of loss to follow-up was explored by comparing depression prevalence and MVPA levels in those who did not participate in the age 46 (BCS70) or 50 (NCDS58) waves.

3. Results

3.1. Sample characteristics

Depression prevalence was 13.9 % in BCS70 and 6.4 % in NCDS58 at

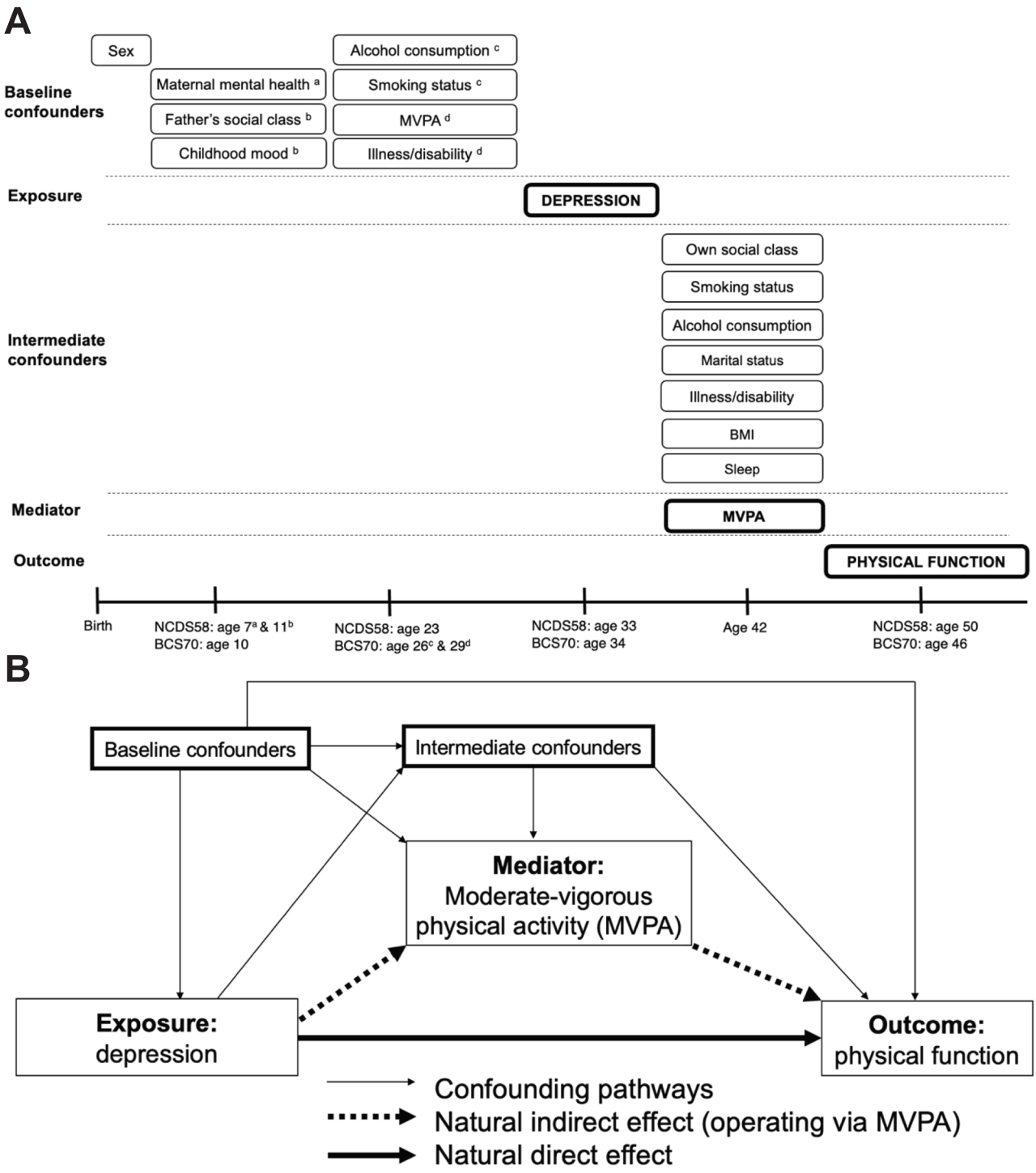

Fig. 2. A. Overview of temporality of all variables included in the model; B. simplified directed acyclic graph of hypothesised pathways between depression and physical function.

ages 34 and 33, respectively. BCS70 participants were consistently more active than NCDS58 participants; for example, at age 42, 72.8 %% of the BCS70 sample participated in MVPA ≥1/week compared to 44.0 % in NCDS58. BCS70 and NCDS58 participants had similar physical function scores at ages 46 and 50 (median: 95 (Quartile 1: 85, Quartile 3: 100) in both). Characteristics of all covariates are described in Table 1.

3.2. Regression results

Table 2 outlines all regression results for: i) depression and MVPA (exposure → mediator); ii) MVPA and physical function (mediator → outcome); and iii) depression and physical function (exposure → outcome). In sex-adjusted models, those with depression had 23.2 % (−28.4,-18.0) and 21.1 % (95%CI: −25.0,-17.2) lower physical function scores in NCDS58 and BCS70, respectively (Model 1i). Estimates were only partially attenuated after adjustment for baseline confounders (−19.2 % (−24.3,-14.0) in NCDS58; −16.4 % (−20.3,-12.5) in BCS70; Model 2i).

Greater MVPA frequency was associated with better physical function in both cohorts. Notably in both cohorts, there was a non-linear

Table 2
Associations between depression, moderate-vigorous physical activity (MVPA) and physical function using logistic regressions in NCDS58 and BCS70.

Association of interest	Independent variable	Dependent variable	Regression type (estimate presented)	Model 1	Model 2
NCDS58 (n = 7278)					
i) Exposure, 33y → Outcome, 46y	Depression: no (ref)	Physical function	Linear regression (β coefficient)[a]	-	-
	yes			−23.2 % (−28.4, −18.0)	−19.2 % (−24.3, −14.0)
ii) Mediator, 42y → Outcome, 46y	MVPA: <1 day/week (ref)	Physical function [a]	Linear regression (β coefficient)[a]	-	-
	1 day/week			7.1 % (3.2, 11.1)	5.4 % (1.4, 9.3)
	2-3 days/week			9.9 % (6.4, 13.5)	7.8 % (4.3, 11.3)
	4-5 days/week			10.4 % (5.1, 15.6)	7.8 % (2.5, 13.1)
	6-7 days/week			4.9 % (0.3, 9.4)	4.1 % (−0.5, 8.6)
iii) Exposure, 33y → Mediator, 42y	Depression: no (ref)	MVPA[b]: <1 day/week (ref)	Multinomial logistic regression (RR)	-	-
	yes	1 day/week		0.99 (0.74, 1.33)	1.12 (0.83, 1.50)
		2-3 days/week		0.63 (0.47, 0.86)	0.75 (0.55, 1.02)
		4-5 days/week		0.58 (0.36, 0.95)	0.72 (0.44, 1.18)
		6-7 days/week		1.25 (0.92, 1.69)	1.36 (1.00, 1.85)
BCS70 (n = 6097)					
i) Exposure, 34y → Outcome, 46y	Depression: no (ref)	Physical function[a]	Linear regression (β coefficient)[a]	-	-
	yes			−21.1 % (−25.0, −17.2)	−16.4 % (−20.3, −12.5)
ii) Mediator, 42y → Outcome, 46y	MVPA: <1 day/week (ref)	Physical function[a]	Linear regression (β coefficient)[a]	-	-
	1 day/week			12.1 % (7.5, 16.7)	9.6 % (5.0, 14.1)
	2-3 days/week			14.2 % (10.6, 17.7)	11.5 % (8.0, 15.1)
	4-5 days/week			11.6 % (7.5, 15.7)	9.9 % (5.8, 14.1)
	6-7 days/week			6.4 % (1.9, 10.9)	6.5 % (2.0, 11.0)
iii) Exposure, 34y → Mediator, 42y	Depression: no (ref)	MVPA[b]: <1 day/week (ref)	Multinomial logistic regression (RR)	-	-
	yes	1 day/week		0.68 (0.53, 0.88)	0.74 (0.58, 0.96)
		2-3 days/week		0.60 (0.50, 0.73)	0.67 (0.55, 0.81)
		4-5 days/week		0.57 (0.45, 0.72)	0.60 (0.48, 0.77)
		6-7 days/week		0.77 (0.61, 0.98)	0.77 (0.60, 0.98)

MVPA: moderate to vigorous physical activity; CI Confidence Interval; RR: Relative Risk ratio.
Model 1: Sex-adjusted (no interactions present).
Model 2: adjusted for sex, father's social class (NCDS58: age 11, BCS70: age 10), maternal mental health (NCDS58: age 7, BCS70: age 10), mood (NCDS58: age 11, BCS70: age 10), alcohol consumption (NCDS58: age 23, BCS70: age 26), smoking habits (NCDS58: age 23, BCS70: age 26), long-standing illness/disability (NCDS58: age 23, BCS70: age 29), MVPA (NCDS58: age 23, BCS70: age 29).
[a] Beta coefficient indicates percent difference in physical function (95 % CI).

Table 3
Mediation results (total causal effect, randomised analogues of the natural direct and indirect effects, total proportion mediated) in BCS70 and NCDS58.

	NCDS58 (n = 7278)[c]	BCS70 (n = 6097)[c]
Ref: No depression		
Total causal effect (TCE)	−19.0 % (−26.0, −12.0)	−16.3 % (−21.1, −11.5)
Randomised analogue of the natural direct effect (rNDE; not via MVPA)[a]	−18.8 % (−25.8, −11.8)	−15.8 % (−20.6, −11.0)
Randomised analogue of the natural indirect effect (rNIE; via MVP)[b]	−0.2 % (−0.6, 0.3)	−0.5 % (−1.0, −0.03)
Total proportion mediated (%)	0.9 % (−1.6,3.4)	3.1 % (0.1, 6.0)

[a] Association between depression and physical function, not mediated by MVPA (thick line in Fig. 2).
[b] Association depression and physical function, mediated by MVPA (dashed line in Fig. 2).
[c] Model adjusted for all baseline [sex, father's social class (NCDS58: age 11, BCS70: age 10), maternal mental health (NCDS58: age 7, BCS70: age 10), mood (NCDS58: age 11, BCS70: age 10), alcohol consumption (NCDS58: age 23, BCS70: age 26), smoking habits (NCDS58: age 23, BCS70: age 26), long-standing illness/disability (NCDS58: age 23, BCS70: age 23), and intermediate [MVPA, own social class, alcohol consumption, smoking habits, marital status, BMI, long-standing illness/disability and sleep (all at age 42 in both cohorts)] confounders.

association such that those who participated 1, 2–3 or 4–5 days/week were more likely to have better physical function than those who did <1 day/week of MVPA, however there was a smaller effect for those who did 6–7 days/week across all models (Table 2, Models 1-2ii).

In both sex and baseline confounder-adjusted models in BCS70, individuals with depression were more likely have lower MVPA levels, compared to those with no depression (all relative risk ratios (RR) <1; Model 1-2iii). In NCDS58, there was a similar but weaker pattern. Additionally, there was some evidence to suggest that depression was associated with greater likelihood of exercising 6–7 days/week (RR: 1.36 (1.00, 1.85); Model 2iii.

3.3. Mediation analysis

The TCE of depression on physical function, expressed as symmetric percent differences, was −19.0 % (−26.0,-12.0) in NCDS58 and − 16.3 % (95 % CI: −21.1,-11.5) in BCS70 (Table 3). In BCS70, this was partitioned into a rNDE of −15.8 % (−20.6,-11.0; i.e. not acting via MVPA) and a rNIE of −0.5 % (−1.0,-0.03; i.e. acting via MVPA). In NCDS58, the direct effect was slightly larger (rNDE: −18.8 % (25.8, −11.8)), however there was little evidence of an indirect effect (rNIE: −0.2 % (−0.6,0.3). Therefore, the total proportion mediated was 3.1 % (0.1,6.0) in BCS70 and 0.9 % (−1.6,3.4) in NCDS58.

3.4. Sensitivity analysis

In the first sensitivity analysis, where MVPA at age 46 instead of age 42 was modelled as the mediator in NCDS58, regression associations largely did not change (Supplementary Table 3), with comparable mediation estimates: TCE of −21.9 %(−31.5,-12.3), rNDE of −21.7 % (−31.3,-12.1), a rNIE of −0.1 %(−0.7,0.4), and a total proportion mediated of 0.7 %(−1.9,3.3). In the second sensitivity analysis, when binary mediators of low MVPA and high MVPA were used instead of the five-level nominal variable, results indicated that mediation was driven by low MVPA levels in BCS70. In BCS70, the total proportion mediated was 4.9 %(1.5,8.2) for low MVPA and 1.4 % (−1.0,3.7) for high MVPA. There remained no evidence of mediation in NCDS58 (low MVPA: 1.4 % (−1.1,3.8); high MVPA: 0.8 %(−1.6,3.2)). Finally, those included in the analytical sample were less likely to have depression (13.9 % vs 18.2 % in BCS70; 6.4 % vs 9.9 % in NCDS58) and marginally more likely to participate in more MVPA (72.8 % v 69.7 % in BCS70; 44.0 % vs 39.0 % ≥1 day/week) than those lost to follow-up.

4. Discussion

In two large British birth cohort studies, we found strong evidence that depression and lower levels of MVPA in early-mid adulthood were associated with higher risk of poor physical function in midlife. Despite robust associations between each of depression, lower MVPA frequency and worse physical function, there was only minimal evidence to indicate that MVPA mediated the relationship between depression and physical function. The total proportion mediated was 3.1 % (0.1, 6.0) in BCS70 and 0.9 % (−1.6,3.4) in NCDS58.

4.1. Depression and physical inactivity as risk factors for poor physical function

Our results indicated that depression and physical inactivity in early adulthood are risk factors for poor physical function in midlife, independent of lifetime socioeconomic position, marital status, childhood and familial mental health, health behaviours (e.g. alcohol consumption, smoking habits, sleep habits) and other markers of physical health (e.g. BMI, illness/disability). Depression has long been recognised as a major risk factor for poor physical function (McKnight & Kashdan, 2009; Stuck et al., 1999) and addressing depressive symptoms, via early clinical treatment, has been shown to directly improve functional outcomes (Callahan, Kroenke, Counsell, et al., 2005; Habert, Katzman, Oluboka, et al., 2016). Potential mechanisms of the depression-physical function relationship include low social engagement, occupational disruptions, financial, household or social strain, increased inflammation or physical inactivity (Gayman, Turner, & Cui, 2008; McKnight & Kashdan, 2009).

Therefore, it was also unsurprising to observe positive association between MVPA frequency and physical function. Increasing aerobic and resistance training in middle and older aged adults can directly improve functional outcomes (Chase, Phillips, & Brown, 2017; Di Lorito, Long, Byrne, et al., 2021; Dipietro, Campbell, Buchner, et al., 2019; Dugan, Gabriel, Lange-Maia, & Karvonen-Gutierrez, 2018; Paterson & Warburton, 2010). Participation in strenuous exercise yields benefits across cardiometabolic and musculoskeletal systems, while inactivity contributes to increased inflammation and adiposity (Lang, Guralnik, & Melzer, 2007; Paterson & Warburton, 2010); deficiencies in any of these areas can cause impaired physical function (Norris, Blodgett, Rogers, Hamer, & Pinto Pereira, 2022). Despite a positive association between MVPA and physical function, there was minimal support for a dose-response relationship, with some indication that MVPA was less beneficial in those engaging in daily exercise (e.g. 6-7 days/week). This may be a result of a threshold effect, where benefits may be maximised at 75–150 min/week, or a reverse J-shaped curve, where musculoskeletal and cardiometabolic benefits are lost as a result of excessive MVPA (Ekelund, Tarp, Steene-Johannessen, et al., 2019; O'Keefe & Lavie, 2013; O'Keefe, O'Keefe, & Lavie, 2018).

4.2. Depression and physical inactivity

As commonly observed in clinical and community-dwelling samples (Schuch et al., 2017; Vancampfort et al., 2017), individuals with depression participated in MVPA less frequently. An estimated 65–88 % of individuals with major depressive disorder do not meet the recommended weekly guidelines of 150 min of MVPA (Schuch et al., 2017), highlighting the extent of this problem. Barriers to exercise in individuals with depression include low mood, low self-efficacy, low energy, high stress and a lack of support (Firth et al., 2016; Vancampfort, Stubbs, Sienaert, et al., 2015). It is important to acknowledge the non-linear association; those with depression were as likely (BCS70) or slightly more likely (NCDS58) to participate in MVPA 6–7 days/week than those without. Excessive engagement in MVPA may be a coping mechanism for those with depression, due to the positive impact of increased β-endorphins or improved mood post-exercise, although distraction and positive self-efficacy hypotheses have also been proposed (Craft, 2005; Faulkner, Rhodes, Vanderloo, et al., 2020; Vancini, de Lira, & Arida, 2013). We must examine if excessive levels of MVPA in some individuals with depression is replicated in other population-representative cohorts.

4.3. Physical inactivity as a mediator between depression and physical function

Despite the well-defined pathways between depression, MVPA and physical function outlined above, there was minimal evidence that MVPA mediated the association between depression and physical function. With two birth cohorts, we must be cautious when speculating on secular trends, however it is notable that there was no mediation effect in those born in 1958, with a small effect in those born in 1970. Given that both reported prevalence of depression (Liu et al., 2020) and engagement in leisure time and MVPA (Knuth & Hallal, 2009; Stamatakis, Ekelund, & Wareham, 2007) have risen over the past few decades, the role of MVPA in mediating depression and physical function may be evolving. The proportion mediated in BCS70 (3 to 5 %) is considerably weaker than the 7.5 % mediated effect observed in, to our knowledge, the single previous study that has investigated this mediation pathway (Ohrnberger et al., 2017). It is possible that the lower proportion mediated observed here was due to differences in ascertainment of key constructs – Malaise Inventory vs Centre for Epidemiological Studies Depression scales, SF-36 vs Activities of Daily Living, self-reported exercise frequency vs categorical PA intensity of none, mild, moderate, vigorous –, different mediation approaches (parametric g-computation vs path analysis), different covariate selection or other diverging study characteristics such as age or cohort representativeness. In particular, it is possible that MVPA becomes a more important mediator in later life as physical function deficits become more common.

Given that MVPA explained a negligible part of the relationship between depression and physical function, we must consider other mediators. Previous work by Ohrnberger et al. (Ohrnberger et al., 2017) suggested that PA was the strongest mediator, with minimal evidence of social interaction and no evidence of smoking as other potential pathways. The MVPA measure used in this study may not have captured the most applicable aspects of PA. For example, other health outcomes have considered the role of varying PA types, intensities, durations and bouts as well as other 24-h behaviours such as sleep or sedentary behavior (Rollo, Antsygina, & Mark, 2020). Further exploration of other aspects of daily movement as potential mediators is needed. Additionally, lifetime accumulation of depressive symptoms is associated with greater risk of premature mortality than single occurrence (Archer, Kuh, Hotopf, Stafford, & Richards, 2020), a pathway that is hypothesised to be mediated by poor physical health (Houle, 2013). Given the strength of the direct effect of depression on PF, there is a need to further investigate how repeated prevalence of depression may differentially increase risk of poor PF.

4.4. Implications and next steps

This study highlighted the robust associations between depression, MVPA and physical function in midlife. Despite established evidence indicating that midlife is a critical period for declining physical function, with strong links to premature mortality (Cooper, Strand, Hardy, Patel, & Kuh, 2014; Karvonen-Gutierrez & Strotmeyer, 2020), there remains insufficient consideration of midlife physical function in both research and clinical settings. There is an urgent need to expand the focus from older adults aged 65+ to those in midlife as well. Notably, PA programs are considered the most promising interventions to address physical function problems in midlife (Karvonen-Gutierrez & Strotmeyer, 2020) but there are few MVPA interventions specifically targeting those with clinical diagnoses of mental health disorders. Finally, from a research perspective, there is insufficient examination of how diverse aspects of PA (e.g. type, intensity, duration, bout) may mediate the mental-physical health relationship. Many longitudinal cohorts have existing data on depression, PA and functional outcomes; further utilisation of this data, such as applying the parametric g-computation mediation approach, can shed more light on potential pathways.

4.5. Strengths and limitations

The main strengths of this study originate from the two large age-homogenous, nationally representative birth cohort studies. Notably, both cohorts had prospectively ascertained exposures, mediator, covariates and outcomes with strong comparability of measures across construct and time. A subscale of the SF-36, a validated scale widely used in population cohort research, was used to measure physical function at a single age in midlife for each cohort (Obidoa, Reisine, & Cherniack, 2010; Syddall, Martin, Harwood, Cooper, & Aihie, 2009). A major strength is the parametric g-computation mediation approach, which allowed for confounders across multiple ages to be accounted for within the model. Several limitations must also be acknowledged. As required for the counterfactual approach, a cut-point was applied to dichotomise the depression variable. This cut-point (Ploubidis & Cogo-Moreira, 2019; Johnson, 2015) may have under- or overestimated depression in some individuals and reduced the sensitivity of the variable. Differences in cohort characteristics should be interpreted with caution due to differences in ascertainment of measures. It is preferable for the intermediate covariates to be ascertained prior to the mediator, but as temporality of data collection did not allow this in BCS70, intermediate covariates and the mediator were all measured at age 42. The sensitivity analysis in the NCD58 cohort suggested that this had no impact, but it is not clear how this may have impacted BCS70 results. As with any large ongoing cohort study, loss to follow-up is inevitable; higher prevalence of depression in those lost to follow-up suggests that associations could have been underestimated, while those will greater severity of depression may have also been less likely to attend data collection at age 33/34. Finally, ascertainment of MVPA relied on two self-reported questions to estimate the intensity and frequency of exercise; the construct validity of the self-reported measure may have been further exacerbated by the subjective nature of what constitutes strenuous 'sweaty' and 'out of breath' exercise. However, we note that there was a moderate correlation ($r = 0.29$) between device-measured MVPA and the self-reported question at age 46 in BCS70.

5. Conclusion

We found consistent evidence that depression was linked to lower MVPA participation and lower physical function in midlife. Although less frequent MVPA was also linked to worse physical function, there was only minor evidence that MVPA mediated the relationship between depression and PF. Association were stronger in those born in 1970 compared to 1958 and highlights a need for further research in newer cohorts. Most notably, we must expand beyond MVPA to encapsulate

other aspects of PA, and investigate how all movement across the day – e.g. sedentary behavior, sleep – play a role.

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Author contributions

All authors conceived the idea. SPP and TN advised on the statistical analysis. JMB performed all analyses and wrote the initial draft. All authors contributed to the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

The datasets supporting the conclusions of this article are available in the UK Data Service repository [1970 British Cohort Study: https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200001 and National Child Development Study https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=2000032].

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Appendix A. Supplementary data

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