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RESEARCH ARTICLE

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Within-day bidirectional associations between physical activity and affect: A real-time ambulatory study in persons with and without depressive and anxiety disorders

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Abstract

Background: Ambulatory assessments offer opportunities to study physical activity level (PAL) and affect at the group and person-level. We examined bidirectional associations between PAL and affect in a 3-h timeframe and evaluated whether associations differ between people with and without current or remitted depression/anxiety.

Methods: Two-week ecological momentary assessment (EMA) and actigraphy data of 359 participants with current ($n = 93$), remitted ($n = 176$), or no ($n = 90$) Composite International Diagnostic Interview depression/anxiety diagnoses were obtained from the Netherlands Study of Depression and Anxiety. Positive affect (PA) and negative affect (NA) were assessed by EMA 5 times per day. Average PAL between EMA assessments were calculated from actigraphy data.

Results: At the group-level, higher PAL was associated with subsequent higher PA ($b = 0.109$, $p < .001$) and lower NA ($b = −0.043$, $p < .001$), while higher PA ($b = 0.066$, $p < .001$) and lower NA ($b = −0.053$, $p < .001$) were associated with subsequent higher PAL. The association between higher PAL and subsequent lower NA was stronger for current depression/anxiety patients than controls ($p = .01$). At the person-level, analyses revealed heterogeneity in bidirectional associations.

Conclusions: Higher PAL may improve affect, especially among depression/anxiety patients. As the relationships vary at the person-level, ambulatory assessments may help identify who would benefit from behavioral interventions.

KEYWORDS

actigraphy, anxiety disorders, depressive disorders, ecological momentary assessment

1 | INTRODUCTION

Physical activity has gained importance in the management of affective disorders (Zschucke et al., 2013), as an effective (add-on) treatment (Schuch et al., 2016) and preventive factor for a new onset (Hu et al., 2020). Physical activity may also play a role in maintaining mood homeostasis (Chan et al., 2019). A potential mechanism is that mood homeostasis, for example, stabilization of one's mood through engaging in mood-modifying activities such as physical activity or exercise, is thought to be impaired in depression (Taquet et al., 2020). Mobile technologies such as actigraphy devices and smartphones offer new opportunities to study the bidirectional longitudinal association between momentary assessed physical activity and mood states (i.e., positive and negative affect) on a fine-grained time scale in patients' daily environment. This may increase our understanding of the role of physical activity in mood homeostasis, especially relevant in persons with affective disorders.

Actigraphy, which measures physical activity using a wrist-worn device, provides objective and high-density measurements of a person's physical movement in their living environments (Martin & Hakim, 2011). Studies have shown that low physical activity level assessed with actigraphy is linked to affective disorders (Burton et al., 2013), including depression (Minaeva et al., 2020) and anxiety as was shown in our own sample (Difrancesco et al., 2019). Ecological momentary assessment (EMA) provides detailed and frequent information on daily variations in mood and affect (Aan het Rot et al., 2012) that could influence systems regulating physical activity. Studies employing EMA have shown that persons with a current depressive disorder diagnosis have higher instability of negative and positive affect than persons without a diagnosed disorder (Aan het Rot et al., 2012; Schoevers et al., 2020). However, although the relationship between physical activity and affect has been studies before, the association between physical activity and positive and negative affect with mobile technology has not often been investigated. Merikangas et al. (2019) have found a negative unidirectional association between physical activity and subsequent sad mood and the association was stronger in persons with a lifetime diagnosis of bipolar I disorder versus healthy controls. The study was, however, limited by a relatively small sample size of 91 persons with depressive disorders who were lifetime rather than current cases, making it impossible to distinguish trait versus state effects.

Another advantage of mobile technologies is that they allow to study the within-person association between physical activity and affect and their relationships at the individual level (also known as idiographic approach). Studies using ambulatory assessment tools and idiographic methods have shown that patterns in the association between physical activity and affect (Rosmalen et al., 2012) and between physical activity and stress (Burg et al., 2017) may differ widely across persons. As a consequence, not all persons may benefit of physical activity to improve their mood and to lower their stress level. As personalized approaches in psychiatry have shown that smartphone-based micro-interventions can elicit short-term mood changes (Meinlschmidt et al., 2016), the use of mobile technologies may play a role in personalizing treatment via direct feedback of actigraphy devices and apps assessing positive and negative affect.

The aim of this study was to investigate the bidirectional longitudinal association—at the group and individual level—between physical activity and affect assessed using mobile technologies, and whether these associations differ in persons without and with current or remitted depression and/or anxiety disorder diagnoses. As depression and anxiety are highly comorbid disorders (Lamers et al., 2011; Rodney et al., 1997) and we have previously shown that low physical activity level may be a general feature of depression and anxiety (Difrancesco et al., 2019; Hiles et al., 2017), we used data from The Netherlands Study of Depression and Anxiety (NESDA) which includes persons without and with current or remitted depressive and/or anxiety disorders. According to previously published studies, we hypothesize that there is a bidirectional longitudinal association between physical activity and affect at the group level (Chan et al., 2019). As group design studies and single subject-studies have different contributions to the field (Zuidersma et al., 2020) and despite the current urge for personalized patient care (Herrman et al., 2022) single-subject studies are underrepresented we will also conduct explorative analyses on individual level as well.

2 | METHODS

2.1 | Enrollment, intake, and ambulatory assessment

Participants from NESDA were selected to participate in the EMA & Actigraphy sub-study (NESDA-EMAA). Details about NESDA have been provided extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. NESDA participants were initially included at the baseline assessment in 2004–2007 ($n = 2981$), and seen for the fifth time at the 9-year follow-up assessment wave (2014–2017, $n = 1776$) for a follow-up interview. At that time, also 367 siblings of NESDA participants were added, bringing the 9-year follow-up sample to 2143 subjects. At this wave, 384 participants enrolled for the EMAA sub-study. The NESDA study, including NESDA -EMAA, was approved by the VUmc ethical committee (Reference Number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA sub-study. See for a flowchart and details of the NESDA-EMAA in our previous work (Difrancesco et al., 2019; Schoevers et al., 2020). NESDA is also one of the sites that is member of the Motor Activity Research Consortium for Health (Scott et al., 2017). Participants of the NESDA-EMAA study were asked to fill out the EMA assessment, which is an electronic diary, on their smartphone and wore a wrist-worn actigraphy device (GENEActiv, Activinsights Ltd.) for 14 days. In case participants did not possess a smartphone, or their phone was not suitable for participation (e.g., no internet bundle), a smartphone was provided for the duration of the study ($n = 107$, 27.9%).

Participants of the EMA assessment completed a set of items 5 times a day (i.e., every 3 h; fixed design with a personalized timing of assessments to fit participant's natural wake-sleep rhythm; Schoevers et al., 2020). Participants wore the wrist-worn GENEActiv actigraphy device on their nondominant wrist, day and night.

2.2 | Assessment of depressive and/or anxiety disorders and antidepressant use

As in the previous waves, at the 9-year follow-up, DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia, and generalized anxiety disorder) were established with the Composite International Diagnostic Interview (CIDI, version 2.1)(Wittchen, 1994), a highly reliable and valid instrument for assessing depressive and anxiety disorders. Participants were categorized into three groups: (1) a group with no lifetime depressive and/or anxiety disorders, (2) a group with remitted depressive and/or anxiety disorders (having a lifetime, but not current (6 months) diagnosis), and (3) a group with current depressive or anxiety disorder in the past 6 months.

Antidepressant use was based on drug container inspection, and medications were coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Antidepressant use was considered present if participants reported using it more than 50% of the time. Antidepressants included were selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressant (TCA, ATC code N06AA) and other antidepressants (ATC codes N06AF, N06AG, N06AX). Antidepressant use was modeled as a dichotomous (yes/no) variable.

2.3 | Ambulatory assessment variables

2.3.1 | Positive and negative momentary affect states

EMA questionnaires were assessed five times a day and had up to 31 items per time point. They contained both momentary affect state items and other items on activities, context and lifestyle. To assess momentary affect states, items covering high and low arousal, positive and negative momentary affect states were used from the Uncovering the Positive Potential of Emotional Reactivity study (Bennik, 2015). Included items were: I feel satisfied, relaxed, upset, cheerful, irritated, listless, down, energetic, enthusiastic, nervous, bored, calm, and anxious. All items were rated on a 7-point Likert scale ranging from "1 = not at all" to "7 = very much." A positive affect (PA) subscale was calculated by taking the average of PA items (at this moment I feel satisfied, relaxed, cheerful, energetic, enthusiastic, and calm). Similarly, a negative affect (NA) subscale was calculated by averaging all NA items (at this moment I feel upset, irritated, listless/apathic, down, nervous, bored, anxious).

2.3.2 | Physical activity

Raw actigraphy data was processed with the open source R package GGIR (version 1.5–18) (van Hees, 2017). Minute-to-minute daily actigraphy data were derived per participant by summing 5-s data. The average physical activity (in milli-gravity units) between EMA assessments was calculated for each day and for each participant.

Minutes spent in sedentary behavior (physical activity level <30 milli-gravity (Rowlands et al., 2014)), light physical activity (physical activity level between 30 and 125 milli-gravity) and moderate-to-vigorous physical activity (physical activity level >125 milli-gravity; Kim et al., 2017) between EMA assessments were also calculated for each day and for each participant.

2.3.3 | Covariates: age, sex, and work/school days

Covariates were age, sex and work/school days at the time of the NESDA EMAA substudy. These covariates were selected as they have an established theoretical association with psychopathology and with physical activity levels. Work/school days were identified with information from daily EMA assessment as participants were asked to document their location; if they reported their location to be at school/work at least once during a day it was counted as work/school day.

2.4 | Statistical analyses

2.4.1 | Data cleaning and missing data

Data cleaning steps including handling of missing data were previously described for both EMA (Schoevers et al., 2020) and actigraphy (Difrancesco et al., 2019) data and are further reported in the Supplemental Material. The final sample was composed of 359 (93.5%) participants with on average 64.5 ± *SD* 6.7 valid EMA observations and 13.68 ± *SD* 1.26 valid actigraphy days.

2.4.2 | Statistical testing

The distribution of physical activity and momentary affect states observations stratified by diagnostic groups were visualized with a box plot. As the distribution of observations were skewed, Kruskall–Wallis test was used to test differences between diagnostic groups.

Generalized estimating equation models (GEE) were used to test—at group level—the bidirectional longitudinal association between momentary affect states assessed every 3 h and the between assessments average physical activity adjusting for age, sex, and work days (A summary of the analyses is shown in Figure 1). Therefore, analyses were performed by first using momentary affect states as outcome (Model 1) and then by using physical activity as outcome (Model 2). Physical activity was log transformed to take account of the skewed distribution. Data centering of momentary affect states and physical activity was performed by within-person mean; therefore, estimates in the models indicate the effect of changes in affect and physical activity from the diurnal person-specific mean. The first-order autoregressive working correlation structure was chosen to take into account the within-person correlation over the 2-week observation period.

The same analyses were repeated to test for the moderating effect of current or remitted depressive and/or anxiety disorders. When moderation terms were significant, stratified analyses by diagnostic group were conducted to interpret and visualize the group effect. Specifically, for each diagnostic group, the longitudinal associations between minutes spent in sedentary behavior, light physical activity and moderate-to-vigorous physical activity and momentary assessment states were tested with GEE adjusting for age, sex, and work days. The longitudinal associations were then graphically displayed with a forest plot for interpretation of the results. In addition, the moderating effect of antidepressant use on the longitudinal association between physical activity and subsequent momentary affect states in patients with current depressive and/or anxiety disorders was explored.

For this analyses the moderating effect of time of the day on the bidirectional longitudinal association between momentary affect states and physical activity was also explored.

At the individual level, an analysis was performed to visually explore the heterogeneity in the within-person bidirectional longitudinal associations between physical activity and momentary affect states. A linear regression model was run for each participant and within-person slopes were graphically represented in a forest plot as done before by Burg et al (Burg et al., 2017).

All analyses were performed with the statistical software R Studio (R Studio version 1.2.5033, R version 3.5) and the "gee" library, a $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Demographics, psychopathology, and ambulatory assessment variables

The total sample of 359 individuals had an average age of 49.5 ± *SD* 12.6 years and 63.7% were women. Of the total sample, 93 had current and 176 had remitted depressive and/or anxiety disorders, 90 had no current depressive and/or anxiety disorders. Seventy-one individuals of the total sample (19.7%) used antidepressants. Of the 16,920 total EMA assessments, 32.7% were on work/school days. Figure 1 shows the distribution of the affect and physical activity observations; statistically significant differences were found between diagnostic groups ($p < .001$) (Figure 2).

3.2 | Within-day longitudinal association between physical activity and subsequent momentary affect states

Higher activity level was longitudinally associated with higher positive affect and lower negative affect scores in the following 3 h within the same day (Table 1, Model 1, both *p*'s < .001). When testing the moderating effect of current or remitted depressive and/or anxiety disorders, the main effect of activity remained statistically significant. However, having a current depressive and/or anxiety disorder appeared to moderate the relationship between higher

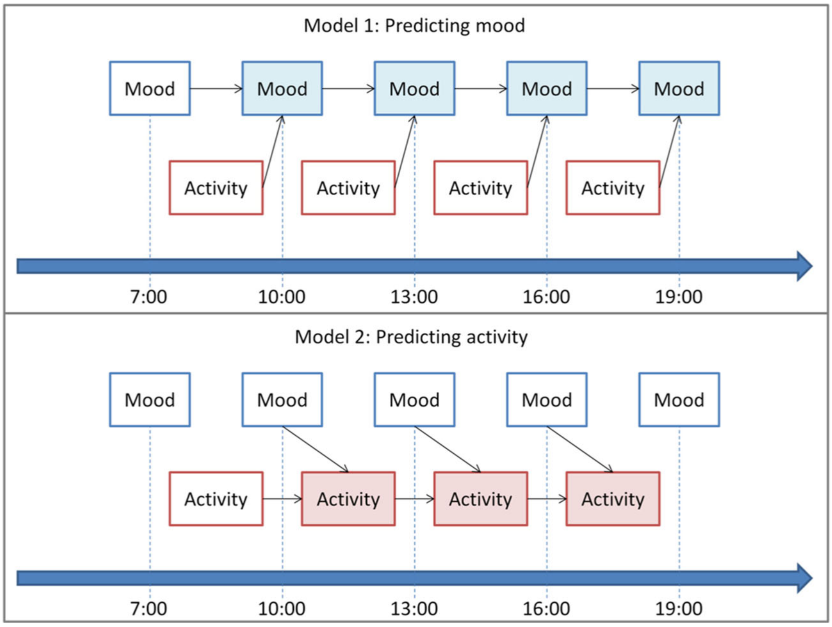

FIGURE 1 Summary of the bidirectional longitudinal association between momentary affect states assessed every 3 h and the average physical activity between assessments. The filled boxes indicate the outcomes

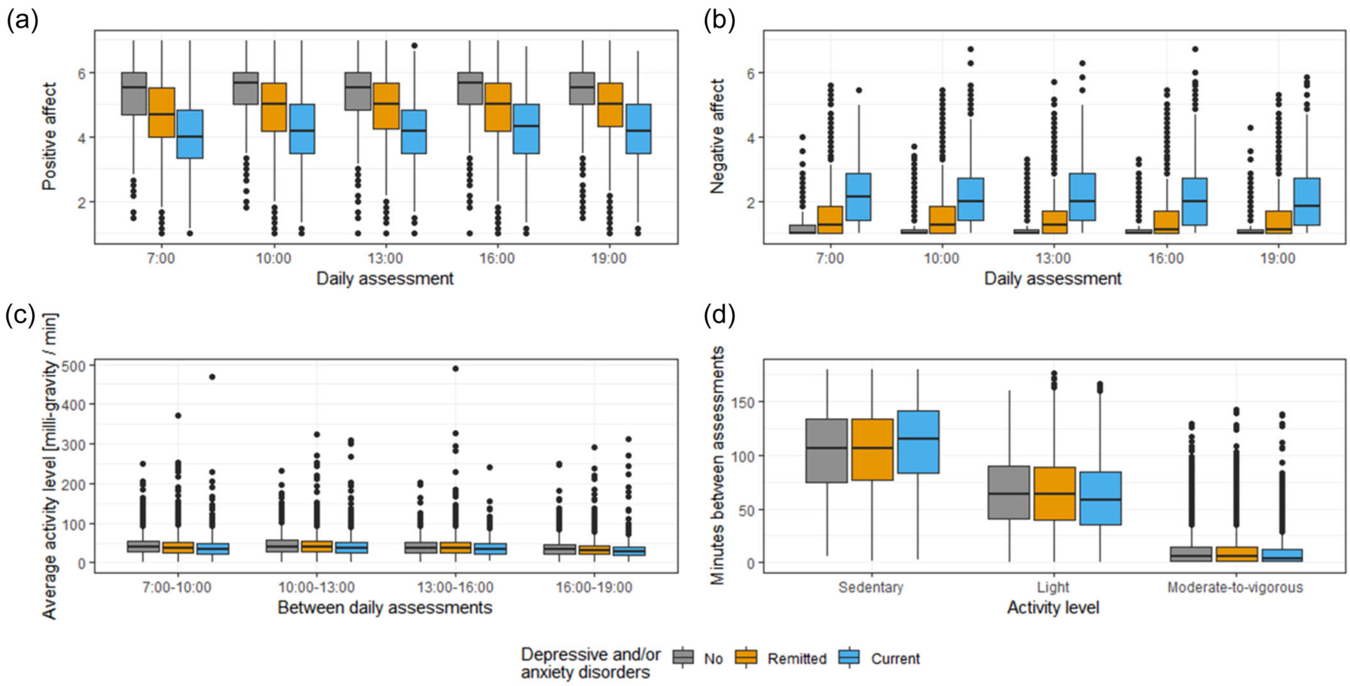

FIGURE 2 Distribution of affect and physical activity observations in the NESDA sample ($n = 359$): positive (a) and negative (b) affect by daily assessment and by diagnosis, activity level between assessments by diagnosis (c) and minutes spent in different activity levels (i.e., sedentary, light, and moderate-to-vigorous) by diagnosis (d). NESDA, The Netherlands Study of Depression and Anxiety

TABLE 1 Bidirectional longitudinal associations between physical activity and momentary affect states ($n = 359$)

	Positive affect			Negative affect		
	B	*SE*	*p*	*B*	*SE*	*p*
Model 1						
Activity (t-1)	0.109	0.014	<.001	−0.043	0.009	<.001
Affect (t-1)						
Positive affect (t-1)	0.336	0.014	<.001			
Negative affect (t-1)				0.360	0.020	<.001
	Activity			**Activity**		
	B	*SE*	*p*	*B*	*SE*	*p*
Model 2						
Affect (t-1)						
Positive affect (t-1)	0.066	0.008	<.001			
Negative affect (t-1)				−0.053	0.011	<.001
Activity (t-1)	0.068	0.013	<.001	0.075	0.013	<.001

Note: Model adjusted for age, sex, and work/school day (details given in the method section).

physical activity level and lower negative affect score, as the interaction term was statistically significant ($p = .010$; Table S1). Having a remitted depressive and/or anxiety disorder appeared to moderate the relationship between higher physical activity level and higher positive affect score, as the interaction term was statistically significant ($p = .033$; Table S1); a similar direction in the association was found in individuals with a current depressive and/or anxiety disorder ($p = .052$; Table S1). As interaction terms were significant, we visualize group effects (Figure 3): a more pronounced positive association was observed between more time spent in light physical activity and moderate-to-vigorous activity level, less time spent in in sedentary behavior and subsequent positive affect for the groups with current and remitted depressive and anxiety disorders. A compatible pattern was observed for negative affect in individuals with current depressive and/or anxiety disorders: less time in sedentary behavior and more time spent in light physical activity and moderate-to-vigorous physical activity were associated with subsequent lower negative affect score. Time of the day did not moderate the relationship between physical activity level and subsequent momentary affect states (results not shown, available upon request). In the current cases, antidepressant use moderated the relationship between physical activity level and subsequent momentary affect states (Table S3, $p = .025$). Higher physical activity level enhanced subsequent positive affect especially in persons taking antidepressants.

Although higher physical activity was associated with subsequent improved affect at the group level, analyses at the person level showed substantial heterogeneity in within-person associations (Figure 4). In some individuals, physical activity decreased positive affect score (within-person slope $b < -0.20$; 14.6% of the total sample) and increased negative affect score (within-person slope $b > 0.20$; 11.6% of the total sample) or had no clear effect.

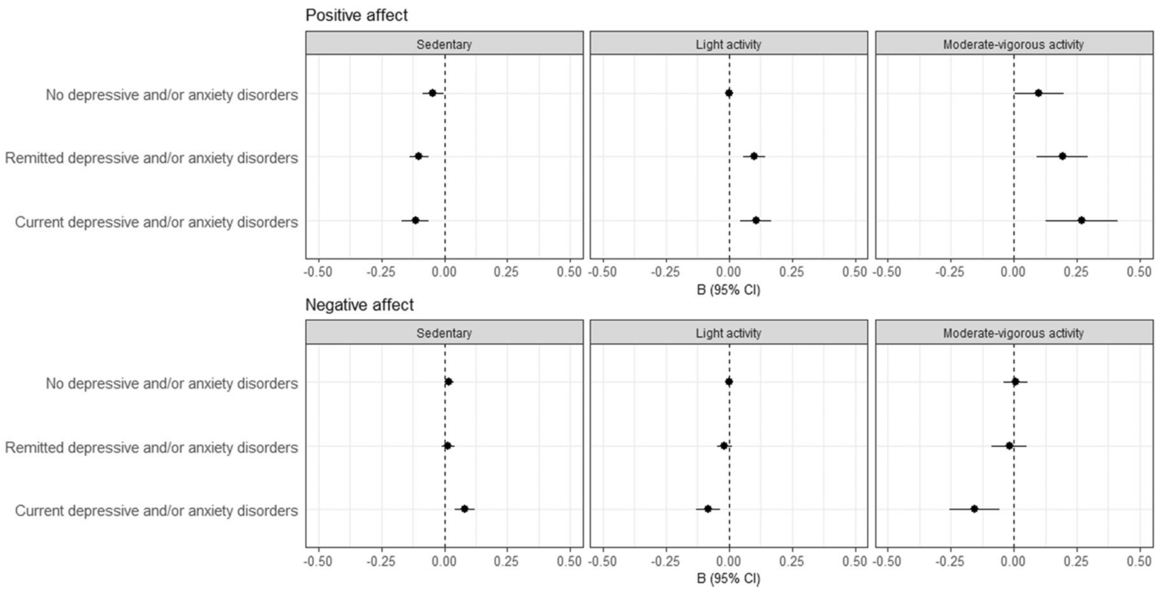

FIGURE 3 longitudinal association between physical activity and subsequent affect (i.e., positive affect and negative affect) stratified by diagnostic group and by time (hours) spent at different activity levels

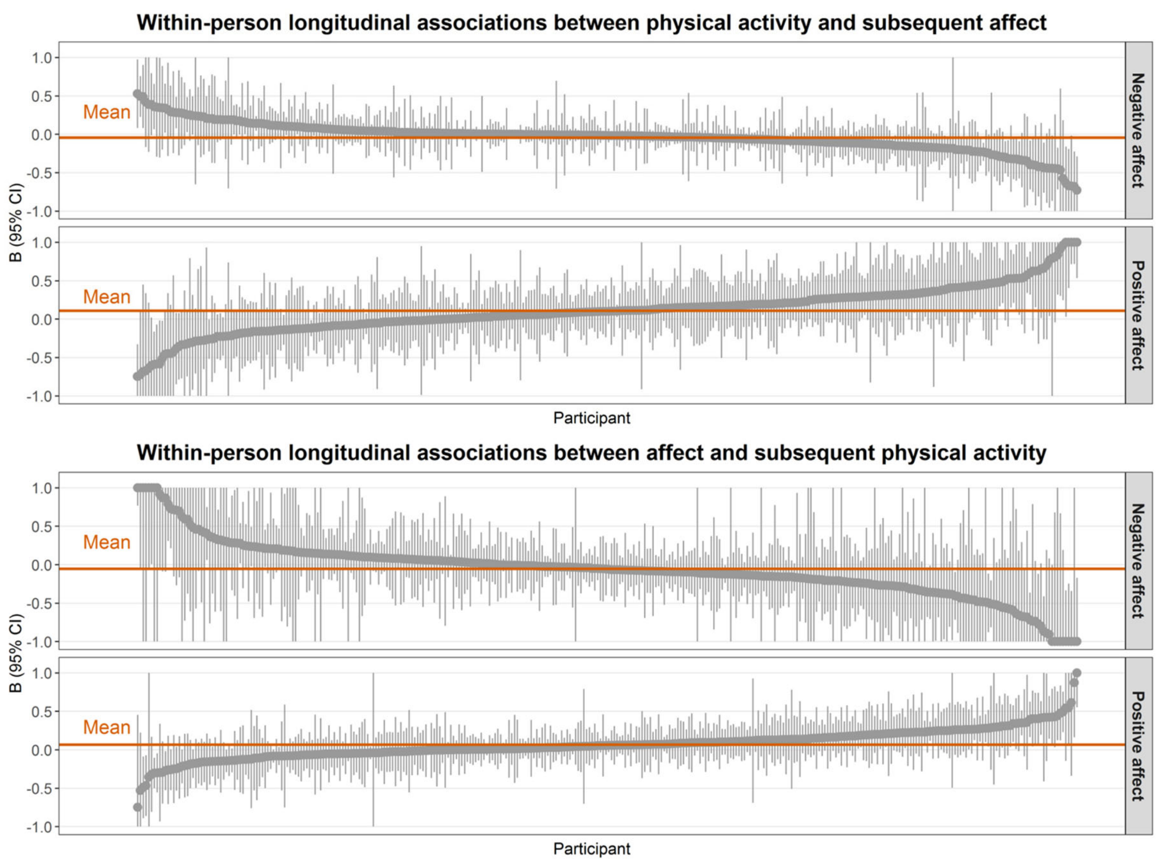

FIGURE 4 within-person slopes of bidirectional longitudinal associations between physical activity and affect

3.3 | Within-day longitudinal association between momentary affect states and subsequent physical activity

Higher score in positive affect and lower score in negative affect were longitudinally associated with higher activity level in the following 3 h (Table 1, Model 2, both $p < .01$). Additionally, when testing the moderating effect of current or remitted depressive and/or anxiety disorders, the main effect remained significant and no interaction (all $p > .05$; Table S2) with current or depressive and/or anxiety disorders was observed. Time of the day did not moderate the relationship between momentary affect states and subsequent physical activity level (results not shown).

Again, analyses at the person level revealed heterogeneity in within-person associations (Figure 4). In some individuals, a negative association between better positive (within-person slope $b < -0.20$; 8.5% of the total sample) and negative (within-person slope $b > 0.20$; 18.5% of the total sample) affect scores and subsequent physical activity were present or no association could be observed.

4 | DISCUSSION

This is one of the first studies to investigate the bidirectional within-day associations between momentary assessed daily activity and affect using mobile technology on a fine-grained time scale in a population with diagnosed current and remitted depression/anxiety disorders and controls. Higher physical activity level was longitudinally associated with improved subsequent affect with enhanced positive affect and reduced negative affect, especially in the group with current depression and/or anxiety. Better mood (i.e., higher positive and lower negative affect) was also associated with subsequent higher activity level. Thus, bidirectional associations between physical activity and affect was confirmed and, highlight the potential of physical activity as a target for mood improvement and regulation in patients with depression and anxiety by breaking the vicious circle. As variability in the within-person association between physical activity and subsequent affect was observed, physical activity may not be effective in enhancing affect in all individual. Ambulatory assessment tools may be useful to personalize physical activity interventions in patients who would benefit most from such interventions.

This study supports and extends previous findings on the bidirectional relationship between physical activity and mood. In line with our results, exercise has been linked to subsequent increased positive affect and decreased negative affect as summarized in the literature review by Chan et al., 2019. Lower activity level has been linked to more sad mood in a sample with lifetime history of bipolar and unipolar depression (Merikangas et al., 2019) using mobile technologies. However, the latter study did not find that mood was related to changes in motor activity, perhaps because of person-level differences in the study sample (Zuidersma et al., 2020). Both psychosocial and neurophysiological mechanisms have been suggested to explain such association such as self-efficacy and the distraction hypothesis, the thermogenic effects and the endorphin theory. Physical activity may lead to improved self-efficacy (i.e., an individual's belief in his or her ability to successfully carry out the necessary action required to satisfy situational demands) and psychological well-being (Barnett, 2013). According to the distraction hypothesis, exercise distracts us from stressful stimuli or offers us a break from daily routine, emancipating us from negative moods (Leith, 1994). The endorphin hypothesis suggests that exercise has a positive effect on mood due to an increased release of β-endorphins following exercise (Bender et al., 2007). The thermogenic hypothesis says that a rise in core body temperature following exercise is responsible for the reduction in symptoms of depression (de Vries, 1981).

Although the effect of mood on subsequent physical activity level has been less studied, there is some literature that is in line with our findings of mood predicting subsequent physical activity. For instance, Liao et al., 2017 has also shown that higher positive affect and lower negative affect are associated with higher moderate-to-vigorous physical activity level in the 15 min after the assessment of affect. By contrast, some studies have also shown no association between mood and subsequent physical activity in persons with unipolar and bipolar disorders (Merikangas et al., 2019) and in persons with depressive and anxiety disorders (Curtiss et al., 2022). These contrasting results may reflect heterogeneity in samples and person-level differences (Zuidersma et al., 2020).

Importantly, higher physical activity level was found to be longitudinally associated with subsequent affect improvement especially in individuals diagnosed with a current depression and/or anxiety disorder. In line with our findings, previous studies have shown that lifetime history of affective disorders moderates the association between physical activity level (Merikangas et al., 2019), daily activities (Taquet et al., 2020) and affect. Possible explanations of why current depression and/or anxiety patients have a stronger coupling of physical activity and subsequent mood than controls could be the following. Persons with depression and/or anxiety may be more sensitive to their daily context (Schoevers et al., 2020) and therefore external changes, such as in their physical activity level or daily activities (e.g., social activities), may impact their mood more strongly. In addition, it has been recently suggested that individuals with a history of depression have impaired mood homeostasis compared to controls, as they have difficulties in stabilizing their mood via mood-modifying activities (Taquet et al., 2020). Physical activity and exercise may therefore be important to target affect in an effort to break a downwards spiral and thus improve mood. On the other hand, for the association of affect predicting subsequent mood, we did not observe differential effects across diagnostic groups, which contradicts the notion of stronger coupling of physical activity and mood in cases versus controls.

However, physical activity may not be beneficial for all individuals with depression and anxiety as shown by the heterogeneity of within-person associations between physical activity and affect. While some individuals experienced a significant beneficial effect of physical activity on affect, others experienced a negative effect or no clear effect. These results may also explain why research on physical activity interventions to treat mental health disorders is often inconsistent and meta-analyses have demonstrated a range of effect sizes and large heterogeneity (Stubbs et al., 2016), and translation of research finding into clinical practice is hampered (Zuidersma et al., 2020). Our results highlight the advantage of using ambulatory assessment tools and idiographic approaches for future research to hopefully improve on effectiveness of physical activity interventions in patients with depression and anxiety. For instance, data collected with actigraphy and EMA could be used to model individual-level associations between affect and physical activity to early identify patients who may benefit from adjunctive behavioral activation to improve their mood.

A question that remains for future studies is the extent to which mobile technologies may assist behavioral interventions to increase physical activity in patients with depression and anxiety. As online psychological interventions have been shown to be effective for psychiatric disorders (Carlbring et al., 2018) and mobile technologies can in real-time monitor patients, mobile technologies may be an add-on tool to online (personalized) psychotherapy. Behavioral activation may be automatically recommended by intelligent algorithms based on physical activity data collected by the wrist-worn actigraphy device of a specific individual. From a broader prospective, when proven effective, mobile technologies may be better integrated into mental health care, given their good social acceptance (Bos et al., 2019) and with relatively lower costs compared to traditional interventions (Olff, 2015). Also, feedback on affect and activity level alone may already help patients by increasing their awareness on how their physical activity and mood are related, as a first step in behavioral change.

This study has limitations. First, the observational study design does not allow to make definitive causal interpretations and to make recommendations for interventions in clinical practice. Second, implementation in clinical practice may be not as straight forward as individual differences in the associations between affect and physical activity are large. Future clinical trials may further investigate the use of idiographic approaches (i.e., individual models) and mobile technologies to provide personalized treatments. This study only focused on the mediating effect of current/remitted depression and/or anxiety and antidepressant use, but other aspects may mediate the relationship between physical activity level and affect, such as comorbid chronic diseases impacting on a person's ability to be physically active. Also, though differences in individual slopes were identified in the current sample, this study did not investigate which factors could explain heterogeneity of such individual associations. Knowledge of which patient characteristics (e.g. sex, age, comorbid somatic disease) and psychiatric clinical characteristics (e.g., type of psychiatric disorder, severity of depression) are linked to positive associations between physical activity and subsequent affect may help to guide whom to offer physical activity interventions. Important strength of the study is the use of mobile technology to study the bidirectional relationship between physical activity and momentary assessed affect on a relatively large sample with CIDI-based depression and anxiety diagnoses.

To conclude, this study has shown a bidirectional association between higher physical activity level and better affect. Increasing physical activity level may become an important target of treatment to improve affect by breaking the downward spiral in patients diagnosed with depression and anxiety. These findings highlight the importance of mobile technologies which capture salient information about subjective experience of affect and objective physical activity level in real-time. The bidirectional association between physical activity and affect can however vary from person to person. We therefore also pointed out the urge of future idiographic research to make mobile technologies useful for clinical practice. Mobile technologies may be used for real-time personalized monitoring of affect and physical activity and to provide feedback to patients. This may increase their awareness on how mood and activity are interlinked, and perhaps increasing patient's self-management skills and support behavioral changes. As mobile technologies are widely used and accepted in patient's daily life, future online psychological interventions such as behavioral activation may integrate in such technologies to provide personalized interventions in patients with depression and anxiety.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

According to European law (GDPR) data containing potentially identifying or sensitive patient information are restricted; our data involving clinical participants are not freely available in a public repository. However, data are available upon request via the NESDA Data Access Committee (nesda@amsterdamumc.nl).

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