Concurrent use of polypharmacy and potentially inappropriate medications with antidepressants in older adults
A nationwide descriptive study in Denmark during 2015–2019
Ishtiak-Ahmed, Kazi; Köhler-Forsberg, Ole; Mortensen, Erik Lykke; Nierenberg, Andrew A.; Gasse, Christiane

Published in:
General Hospital Psychiatry

DOI:
10.1016/j.genhosppsych.2023.03.009

Publication date:
2023

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY-NC-ND

Citation for published version (APA):
A multiple health behaviour change intervention to prevent depression: A randomized controlled trial

Irene Gómez-Gómez, Emma Motrico, Patricia Moreno-Pera, Marc Casajuana-Closas, Tomas López-Jiménez, Edurne Zabaleta-del-Olmo, Ana Clavería, Joan Llobera, Ruth Martí-Lluch, Rafel Ramos, José-Ángel Maderuelo-Fernández, Caterine Vicens, Marta Domínguez-García, Cruz Bartolomé-Moreno, Jose I. Recio-Rodríguez, Juan Á. Bellón

Objective: To examine the effectiveness of a 12-month MHBC intervention in the prevention of onset depression in primary health care (PHC).

Methods: Twenty-two PHC centres took part in the cluster-randomized controlled trial. Patients were randomized to receive either usual care or an MHBC intervention. The endpoints were onset of major depression and any behaviour.

Results: 2531 patients agreed and were eligible to participate. At baseline, around 43% were smokers, 82% were non-adherent to the Mediterranean diet and 55% did not perform enough physical activity. The intervention group exhibited a greater positive change in two or more behaviours (OR 1.75 [95%CI: 1.17 to 2.62]; p = 0.002), while this increase was not statistically significant for smoking and physical activity.

The intervention was not effective in preventing major depression (OR 1.17; [95% CI 0.53 to 2.59]).
1. Introduction

Around 5% of the world’s population suffered from depression in 2019 [1]. In primary health care (PHC), evidence has shown that the prevalence of depression ranged between 8.5% (male) and 13.9% (female) [2]. Depressive disorders rank third for women and fifth for men in global disease burden regarding years lived with disability [3]. Although the treatments available for depression are effective, they only reduce disease burden by <30% [4]. Additionally, depression has substantial economic consequences [5]. In the US, between 2010 and 2018, the incremental economic burden of adults with major depressive disorder increased by 38% from $237 to $326 billion [6]. A way to reduce the burden of depressive disorder is by preventing new episodes in nonclinical populations [7–9] or reducing depressive symptoms [10,11].

Among the strategies available, the promotion of healthy lifestyles may play a crucial role. Recent evidence suggests that lifestyle behaviours may be involved in the development of depressive disorders [12–16]. Thus, the promotion of a healthy lifestyle can be considered a potential approach to the prevention of depression [16] or the reduction of depressive symptoms [11,17]. Low adherence to a healthy diet, physical inactivity, and tobacco use are the most prevalent unhealthy behaviours in many countries [18–20]. Evidence suggests that around 30–40% of the adult population presents a co-occurrence profile of two of these behaviours [18,20–22]. Specifically, 47–54% of the adult population present low adherence to a healthy diet and a low level of physical activity, 23–28% present low adherence to healthy diet and smoking, and 8–20% present low level of physical activity and smoking [23]. These data suggest that multiple health behaviour change (MHBC) interventions may better fit this co-occurrence profile than single behaviour change interventions.

Although there is an increasing number of publications on MHBC interventions [24], it is worthy of note that the study area on MHBC interventions has been undervalued [25]. The same pattern has been found regarding depression. Thus, single-risk lifestyle interventions for preventing depression are more frequent [17,26–28] than MHCB interventions [11,29].

To date, little is known about the effectiveness of MHBC interventions in preventing depression, especially in PHC, which is the ideal setting to implement health promotion and disease prevention activities (M. [30]). PHC is considered the ‘front door’ of the health system [31]. It is estimated that around 83% of people have made at least one visit to their PHC center in the last 12 months [31], with a mean number of visits per year between 0 and 4 [32]. On average, patients with both clinical and subclinical depression visit their PHC center more than four times a year [32]. Regarding the effectiveness of MHBC in preventing depression in PHC, to the best of our knowledge, only three RCTs have been published [33–35]. Two were focused on patients with or at high risk of diabetes [34,35] and one on patients with cardiovascular disease [33]. The studies published by Brotos et al., [33] and Siddiqui et al., [35] showed statistically significant reductions in depressive symptoms during follow-up in the intervention group, as compared to the control group. The MHBC interventions were aimed at promoting physical activity and healthy diet [33], and physical activity, healthy diet and smoking cessation [35] in depressed and non-depressed patients. In contrast, Davies et al., [34] did not find any significant differences between the control and the intervention group in terms of symptoms of depression at the end of a MHBC intervention, which was aimed at promoting a healthy diet and physical activity. We have to note that none of these previous studies excluded patients with major depression at baseline and they did not distinguish between treatment and prevention of depression.

This secondary study assesses whether a MHBC intervention, which promotes the Mediterranean diet, physical activity, and/or smoking cessation, is effective in preventing depression at 12-month follow-up in primary care attenders aged 45–75 years.

2. Methods

2.1. Study design

An effectiveness implementation hybrid cluster randomized phase 2 trial was conducted involving two parallel groups to evaluate the effectiveness of a MHBC intervention implemented in PHC to promote physical activity, high adherence to the Mediterranean diet, and quitting smoking among PHC attenders aged between 45 and 75 years (EIRA study) [36,37]. The study has been reported according to the Consolidated Standards of Reporting Trials (CONSORT) extension for cluster trials [38].

2.2. Participants

The EIRA study was conducted in 26 PHC centers in seven of the 17 Autonomous Communities in Spain (Andalusia, Aragon, the Balearic Islands, Castile and Leon, Catalonia, Galicia and Basque Country). A PHC centre was lost after the pre-implementation stage for reasons related to external policy and lack of resources. Three PHC centers of the Basque Country were excluded due to their failure to assess major depression using the CIDI either at baseline and at follow-up. Finally, 22 PHC centers from six Spanish Autonomous Communities were included in this study. PHC centers were eligible to participate in the study if they had Internet connection, were not located in multicultural and multi-linguistic areas, could implement community activities, and the management team was motivated.

PHC attendees from the 22 PHC centers aged 45–75 years exhibiting at least two unhealthy behaviours (low adherence to the Mediterranean diet, low level of physical activity, and/or smoking) were invited to participate in the study. Specifically, to determine if the participants were physically inactive the Brief Physical Activity Assessment Tool were used [39,40]. Participants were asked two questions about the times per week they practiced at least 30 min of moderate physical activity (from never (0 points) to 5 or more times a week (4 points)) and the times per week they practiced at least 20 min of vigorous physical activity (from never (0 points) to 3 or more times a week (4 points)). To be considered physically inactive, the sum of the scores for both questions had to be ≤3 points. To determine the adherence to the Mediterranean diet evaluated two validated questions about the daily consumption of fruits and vegetables were used [41]. Participants were asked separately about the daily servings of fruits and vegetables (from not all days (0 points) to 5 or more servings per day (4 points)). A score < 4 points derived from the sum of both questions was considered low adherence to the Mediterranean diet. In addition, participants were considered smokers if they reported smoking ≥1 cigarette per day during the last month. Participants were excluded if they had major depression at baseline according to the Composite International Diagnostic Interview (CIDI) [42,43], severe advanced physical illness, cognitive impairment, functional dependence for basic activities of daily living,
severe mental illness, if they were receiving treatment for cancer or end-of-life care, were engaged in a long-term home health care program. Those patients who stated that they were planning to not reside in the area during the year after recruitment were also excluded. There were no restrictions regarding the use of psychotropic medications but participants with bipolar disorder, personality disorder, schizophrenia and other psychotic disorders were excluded from the study.

2.3. Procedures

The EIRA study was conducted from January 2017 to December 2018. PHC centers were computer allocated 1:1 to either usual care or the intervention group at a central location (IDIAPGol, Barcelona, Spain). Participants attended in the PHC centers assigned to the intervention group received a 12-month MHBC intervention to promote adherence to the Mediterranean diet, physical activity, and/or smoking cessation. The participants belonging to the PHC centers assigned to the control group received usual care. All participants signed informed consent prior to participating in the study and before being informed on whether they had been assigned to the control group or the intervention group.

Prior to the initiation of the study, all PHC professionals involved signed a commitment to collaboration. PHC professionals were not blinded to the different experimental conditions. Evaluation measures were taken by non-blinded external evaluators at baseline and follow-up.

2.4. Measures

2.4.1. Baseline measures

Sociodemographic characteristics of the participants such as sex, age, level of education, marital status, employment status, and country of birth were assessed. In addition, information about prevalence and co-occurrence of unhealthy behaviours; symptoms of depression (PHQ-9; [44] Diez-Quevedo et al., 2001); symptoms of anxiety (GAD-7; [45]); social support (Duke-UNC-11; [46]); health-related QoL (EQ-5D-3L; [47]) comorbidities, and body mass index (BMI) were also assessed at individual level. Information was also collected in relation to PHC centers (mean enrolled/assigned population, population age, mean number of PHC practitioners, PHC nurses, and PHC social workers) and PHC professionals (age, sex, time (years) working in PHC, time (years) working in the same PHC center, academic training level and prevalence of healthy behaviours).

2.4.2. Positive change in smoking status, physical activity, and adherence to Mediterranean diet

Positive changes in smoking status were defined as smoking at baseline and not smoking at follow-up and were assessed by self-reported continuous abstinence [48]. Positive changes in physical activity behaviour were defined as having a low level of physical activity at baseline and moderate or high level of physical activity at follow-up according to the 7-item Physical Activity Questionnaire (IPAQ-SF) [49]. Regarding positive change in Mediterranean diet adherence, it was defined as obtaining eight or fewer points at baseline and nine or more points at follow-up on the 14-item Questionnaire of Mediterranean diet adherence (MEDAS) [50]. Both IPAQ and MEDAS have shown good psychometric properties [49,50]. Health behaviour outcomes were assessed at baseline and at 12 months.

2.4.3. Endpoints

Endpoints were cumulative 12-month incidence of the onset of DSM-IV major depression, as measured on the depression section of the CIDI [42,43], and severity of depressive symptoms, as measured on the Patient Health Questionnaire-9 (PHQ-9), which is a 9-item self-reported questionnaire designed to evaluate the presence of depressive symptoms within the prior 2 weeks [51].

CIDI was used to exclude patients with major depressive disorder at baseline. Thus, patients with a diagnosis of major depression according to the CIDI were discarded at baseline. Endpoints were assessed at baseline and at 12 months.

2.4.4. Intervention

The MHBC intervention has been described in detail elsewhere [36,37]. Briefly, the MHBC intervention was based on the Trans-theoretical Model [52] and the 5 As framework [53]. The intervention was administered by PHC professionals (family physicians and nurses). Before the intervention PHC professionals received a 20-h online training, an in-person group feedback session and a role-playing session about motivational interviewing techniques. The intervention had a maximum duration of 12 months and was carried out at three levels: individual, group and community. The individual intervention comprised a minimum of 2–3 sessions. PHC professionals, together with patients, implemented an action plan to promote behaviour change on the basis of patient's stage of motivational readiness to change each behaviour (Mediterranean diet adherence, physical activity and/or smoking cessation). The individual intervention was complemented with additional resources such as health behaviour brochures, access to the EIRA study website (https://proyecto-era.rediapp.org/index.php/proyecto-era), and mobile apps. In addition, patients who consented received personalized SMS to promote Mediterranean Diet, physical activity and smoking cessation. The group approach comprised group sessions of 90–120 min focused on promoting a healthy diet, physical activity and/or smoking cessation. Finally, the patients were prescribed community-type activities (e.g. walks, dance workshops and healthy cooking workshops).

2.4.5. Control

Participants in the control group received treatment-as-usual and attended a baseline assessment and a follow-up assessment.

2.5. Statistical analyses

Statistical analyses were performed with Stata (version 14.2) (Stata Corporation, College Park, TX, USA) and analysed participants according to their randomized treatment. We accounted for missing outcomes using multiple imputations with chained equations [54], under a missing-at-random framework. We generated 50 datasets. Rubin's rules were used to combine estimates from each imputed dataset [55]. Differences between the control and intervention group at baseline by PHC center, PHC professional and patient-level were evaluated through bivariate multilevel mixed-effects linear or logistic regression analysis [56].

To evaluate the effectiveness of the intervention on the cumulative incidence of major depression (CIDI) and the reduction of severity of depressive symptoms (PHQ-9) during the 12-month follow-up, multilevel mixed-effects logistic regression and multilevel mixed-effects linear regression were performed, respectively, for clustered data with the PHC center as a random-effects parameter. To perform multilevel mixed-effects linear regression models, the database was transformed from wide to long and two levels of cluster (time and PHC center) were taken. In turn, we created a time variable (baseline (t0) and follow-up (t2)) as a fixed effect, and introduced it into the model, in addition to time-group interaction. Odds ratios (OR) or adjusted mean difference, Confidence Interval [95% CI] and significance (p-value) were computed. Models were adjusted for symptoms of depression at baseline and for other prognostic predictors: age, sex, quality of life, social support and current comorbidities or status such as symptoms of anxiety and depression [57], as well as diabetes [58,59] hypertension and ischemic cardiomyopathy [60]. In addition, to adjust for selection bias, variables with significant baseline differences between groups were incorporated as covariates (BMI). Additionally, a test of treatment moderation was performed for both outcomes, depressive symptoms and incidence of
depression using the test for the interaction between the assigned group and depressive symptoms (code $0 = 0$ to $4$ PHQ-9 score and code $1 > 4$ PHQ-9 score) at baseline variables.

To know whether those who made more positive health behaviour changes also experienced improvements in depressive symptoms and incidence of depression, a test for the interaction between the assigned group and positive health behaviour changes was performed.

Finally, to know whether those individuals who had more depressive symptoms at baseline differed in their engagement with behavioural health targets, we performed multilevel mixed-effects logistic regression whose dependent variables were positive behaviour changes (yes/no) and using the interaction test for assigned group*depressive-symptoms (code $0 = 0$ to $4$ PHQ-9 score and code $1 > 4$ PHQ-9 score), unadjusted and adjusted for BMI and prognostic predictors of depression.

Fig. 1. Flow diagram of the study participants throughout the study.  
*One PHC centre abandoned after pre-implementation stage due to external policy and lack resources, therefore this PHC centre did.
3. Results

3.1. Baseline characteristics of participants

Eligibilities were evaluated for 4387 patients. A total of 609 and 860 patients from the control and the intervention group were excluded, respectively. Among them, 65 patients in the control group and 79 patients in the intervention group were excluded from the study because they fulfilled the diagnostic criteria for major depressive disorder at baseline. In addition, 249 (control group) and 138 (intervention group) patients from three PHC centers placed in the Basque Country were excluded because major depression was not assessed both at baseline and at follow-up. Thus, 1267 patients in the control group and 1264 patients in the intervention were analysed (Fig. 1).

Regarding participating centers, the mean enrolled population was around 23,000 patients. The mean number of physicians or nurses in the control group was higher than in the intervention group. However, no significant differences were observed in any of the PHC centers variables. Regarding PHC professionals, women accounted for 75.9% and 78.7% in the control and the intervention group, respectively. The average age was around 50 years in the two groups. In addition, the majority of PHC professionals showed good adherence to healthy behaviours. Tables S1 to S2 describe the baseline characteristics of participating centers and PHC professionals (see supplementary material).

At patient level, no significant differences were observed between the control and the intervention group in terms of baseline variables, except for BMI (Table 1). Women accounted for 54.9% and 53.3% in the control and the intervention group, respectively (Table 1). The average age of the patients was 58 years. More than half of the participants in both groups had completed secondary education or higher and around 46% were employed. A total of 67.4% and 73.0% of the participants in the control group and 56.8% in the intervention group, respectively, were married or living with a partner.

Most of the participants in the control (80.5%) and the intervention group (84.4%) had a low adherence to the Mediterranean diet. A total of 52.9% of the participants in the control group and 56.8% in the intervention group were physically inactive, whereas nearly half of the participants in the control group (45.2%) and the intervention group (41.5%) were smokers.

Symptoms of depression at baseline (PHQ-9) were 4.01 (SD = 4.40) in the control group and 4.21 (SD = 4.74) in the intervention group. In addition, 40.7% of the participants in the control group and 51.2% in the intervention group were obese.

3.2. Clustering of health behaviours at baseline

Low adherence to the Mediterranean diet and physical inactivity were observed to have the highest levels of co-occurrence in the control (54.9%) and the intervention group (58.6%) (Table S3, supplementary material). Conversely, the least frequent combination of co-occurrence was smoking and physical inactivity. No significant differences were observed between the control and the intervention group.

3.3. Adherence to the planned intervention

The average number of individual sessions ranged between 0 and 9 sessions (M = 1.24; SD = 1.40) (Table S4, supplementary material). Approximately 41% of patients were smokers at the time of screening, and 90.3% initiated the smoking cessation intervention. Most of patients were at risk of an unhealthy diet (93.4%) at the time of screening, and 89.4% initiated the individual Mediterranean diet intervention. Patients at risk of physical inactivity accounted for 91.5%, of whom 90.2% initiated the individual physical activity intervention. The percentage of patients who were referred to group sessions or community activities was low and ranged between 5.7% and 21.9% and between 1.5% and

### Table 1

Baseline characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 1267)</th>
<th>Intervention group (n = 1264)</th>
<th>Total (N = 2531)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), M (SD)</td>
<td>58.33 (8.22)</td>
<td>57.92 (7.94)</td>
<td>58.13 (8.08)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>572 (45.15)</td>
<td>590 (46.68)</td>
<td>1162 (45.91)</td>
</tr>
<tr>
<td>Female</td>
<td>695 (54.85)</td>
<td>674 (53.32)</td>
<td>1369 (54.09)</td>
</tr>
<tr>
<td><strong>Country of birth, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>1197 (94.46)</td>
<td>1191 (94.21)</td>
<td>2388 (94.34)</td>
</tr>
<tr>
<td>Other countries</td>
<td>70 (5.53)</td>
<td>73 (5.78)</td>
<td>143 (5.66)</td>
</tr>
<tr>
<td><strong>Employment status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>586 (46.22)</td>
<td>585 (46.32)</td>
<td>1171 (46.27)</td>
</tr>
<tr>
<td>Retired</td>
<td>157 (12.36)</td>
<td>153 (12.08)</td>
<td>310 (12.23)</td>
</tr>
<tr>
<td>Other (leave of absence for work, incapacity for work etc)</td>
<td>348 (27.43)</td>
<td>338 (26.73)</td>
<td>685 (27.08)</td>
</tr>
<tr>
<td><strong>Marital Status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/ living with partner</td>
<td>853 (67.36)</td>
<td>923 (73.00)</td>
<td>1776 (70.18)</td>
</tr>
<tr>
<td>Separated/ widowed/ divorced/ single</td>
<td>414 (32.64)</td>
<td>341 (27.00)</td>
<td>755 (29.82)</td>
</tr>
<tr>
<td><strong>Lifestyles variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>572 (45.15)</td>
<td>521 (41.53)</td>
<td>1097 (43.34)</td>
</tr>
<tr>
<td>Non-adherent Mediterranean diet, n (%)</td>
<td>1620 (126.40)</td>
<td>1067 (84.41)</td>
<td>2087 (82.46)</td>
</tr>
<tr>
<td>Insufficiently active, n (%)</td>
<td>671 (52.94)</td>
<td>717 (56.75)</td>
<td>1388 (54.84)</td>
</tr>
<tr>
<td><strong>Psychological variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (PHQ-9), M (SD)</td>
<td>4.01 (4.40)</td>
<td>4.21 (4.74)</td>
<td>4.11 (4.57)</td>
</tr>
<tr>
<td>Anxiety (GAD-7), M (SD)</td>
<td>3.78 (4.28)</td>
<td>3.8 (4.41)</td>
<td>3.81 (4.35)</td>
</tr>
<tr>
<td>Social support (DUKE-11), M (SD)</td>
<td>45.73 (8.14)</td>
<td>46.07 (8.50)</td>
<td>45.90 (8.32)</td>
</tr>
<tr>
<td>Quality of life (EQ-5D), M (SD)</td>
<td>0.84 (0.18)</td>
<td>0.82 (0.19)</td>
<td>0.83 (0.18)</td>
</tr>
<tr>
<td><strong>Other variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal-weight</td>
<td>279 (185.14)</td>
<td>185 (14.67)</td>
<td>464 (18.35)</td>
</tr>
<tr>
<td>Overweight</td>
<td>472 (37.29)</td>
<td>432 (34.15)</td>
<td>904 (35.72)</td>
</tr>
<tr>
<td>Obesity</td>
<td>516 (40.69)</td>
<td>647 (51.17)</td>
<td>1162 (45.92)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>737 (58.16)</td>
<td>735 (58.14)</td>
<td>1472 (58.15)</td>
</tr>
</tbody>
</table>

Note. Analyses were performed by using linear or logistic regression models. *p < 0.05.

12.9%, respectively.

3.4. Effectiveness of the MHBC intervention over positive behaviour change

Table 2 shows the effect of the intervention on positive behaviour change. Greater positive changes in two or three behaviours (OR 1.78; 95% CI 1.19 to 2.65; p = 0.005) and in any behaviour (OR 1.60; 95% CI...
1.16 to 2.23; \( p = 0.006 \) were observed in the intervention group, as compared to the control group, when adjusted for cluster effect. In addition, greater positive changes in diet behaviour were observed in the intervention group, as compared to the control group (OR 1.97; 95% CI 1.30 to 2.97; \( p = 0.001 \)). These differences remain significant when adjusted for not balanced variables at baseline at individual level (BMI). Although there were more positive changes in terms of physical activity and smoking behaviour in the intervention group, compared to the control group, these were not statistically significant.

### 3.5. Effectiveness of the MHBC intervention in preventing the onset of major depression (12-month cumulative incidence)

The intervention was not effective in preventing the onset of major depression at 12-month follow-up either when adjusted for symptoms of depression at baseline (OR 1.35; [95% CI 0.62 to 2.86]; \( p = 0.449 \)) and when adjusted for symptoms of depression and BMI at baseline and for other prognostic predictors for depression (OR 1.17; [95% CI 0.53 to 2.59]; \( p = 0.690 \)).

There were no effect heterogeneity between participants with greater or lower depressive symptoms at baseline in both the unadjusted (OR 1.10; [95% CI 0.48 to 2.50]; \( p = 0.824 \)) and the adjusted (OR 1.29; [95% CI 0.41 to 4.12]; \( p = 0.661 \)) models. Thus, the preventive effect of the intervention was not moderated by the symptoms of depression at baseline.

### 3.6. Effectiveness of MHBC intervention in reducing symptoms of depression

No significant differences were observed between the control and the intervention group regarding depressive symptoms at 12-month follow-up (Mean difference: 0.68; [95% CI -0.90 to 2.10]; \( p = 0.681 \)) (Table 3). These differences remained non-significant when models were adjusted for symptoms of depression and BMI at baseline and for other prognostic predictors for depression (Mean difference: 0.30; [95% CI -0.77 to 1.36]; \( p = 0.726 \)).

There were no effect heterogeneity between participants with greater or lower depressive symptoms at baseline in both the unadjusted (\( \beta = 0.34; [95\% CI -0.40 to 1.08]; p = 0.371 \)) and the adjusted (\( \beta = 0.13; [95\% CI -0.40 to 0.66]; p = 0.621 \)) models. Thus, the effectiveness of the intervention to reduce depressive symptoms was not moderated by the symptoms of depression at baseline.

### 3.7. Effect of experience positive health behaviour changes in preventing the onset of major depression and in reducing symptoms of depression

No evidences were found that achieving more positive changes in two or three behaviour, any behaviour, smoking behaviour, physical

### Table 2

Positive changes of the participants in the intervention group: Mediterranean diet, physical activity and smoking cessation.

<table>
<thead>
<tr>
<th>Positive behaviour change</th>
<th>Control group N = 1267 (n (%))</th>
<th>Intervention group N = 1264 (n (%))</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Positive change in two or three behaviours</td>
<td>123 (9.7)</td>
<td>197 (15.6)</td>
<td>1.72 (1.30 to 2.28)</td>
<td>&lt;0.001</td>
<td>1.78 (1.20 to 2.65)</td>
<td>0.005</td>
<td>1.75 (1.17 to 2.62)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>2 Positive change in any behaviour</td>
<td>576 (45.50)</td>
<td>714 (56.51)</td>
<td>1.56 (1.31 to 1.86)</td>
<td>&lt;0.001</td>
<td>1.60 (1.15 to 2.23)</td>
<td>0.006</td>
<td>1.58 (1.13 to 2.20)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>3 Positive change in smoking behaviour</td>
<td>128 (10.10)</td>
<td>163 (12.88)</td>
<td>1.32 (0.98 to 1.78)</td>
<td>0.065</td>
<td>1.28 (0.85 to 1.94)</td>
<td>0.238</td>
<td>1.31 (0.86 to 1.98)</td>
<td>0.212</td>
<td></td>
</tr>
<tr>
<td>4 Positive change in physical activity behaviour</td>
<td>320 (25.22)</td>
<td>348 (27.53)</td>
<td>1.13 (0.93 to 1.37)</td>
<td>0.234</td>
<td>1.17 (0.77 to 1.77)</td>
<td>0.465</td>
<td>1.14 (0.75 to 1.73)</td>
<td>0.546</td>
<td></td>
</tr>
<tr>
<td>5 Positive change in diet behaviour</td>
<td>262 (20.71)</td>
<td>415 (32.86)</td>
<td>1.97 (1.52 to 2.31)</td>
<td>&lt;0.001</td>
<td>1.97 (1.30 to 2.97)</td>
<td>0.001</td>
<td>1.94 (1.29 to 2.94)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Note. | Adjusted for cluster effect, † Adjusted for cluster effect and not balanced variables at baseline at individual level (BMI).

### Table 3

Effect of the Multiple Health Behaviour Change lifestyle intervention on the reduction of the symptoms of depression (PHQ-9 score).

<table>
<thead>
<tr>
<th>Models</th>
<th>Control Group (n = 1267) Mean (95%CI)</th>
<th>Intervention group (n = 1264) Mean (95%CI)</th>
<th>Mean Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for depressive symptoms at baseline</td>
<td>5.31 (2.25 to 8.36)</td>
<td>5.90 (2.34 to 9.47)</td>
<td>0.60 (0.90 to 2.10)</td>
<td>0.681</td>
</tr>
<tr>
<td>Adjusted for depressive symptoms and BMI at baseline and other prognostic predictors for depression</td>
<td>5.42 (2.35 to 8.49)</td>
<td>5.72 (2.38 to 9.05)</td>
<td>0.30 (0.77 to 1.36)</td>
<td>0.726</td>
</tr>
</tbody>
</table>

Note. Analyses were performed by using multilevel mixed-effects linear regression models. \( \text{age, sex, quality of life, social support and current comorbidities or status such as symptoms of anxiety and depression, diabetes, ischemic cardiomyopathy and hypertension} \). activity behaviour or diet behaviour were associated with greater prevention of the onset of major depression at follow-up (Table S5, supplementary material) or with lower symptoms of depression at follow-up (Table S6, supplementary material).

### 3.8. Influence of depressive symptoms at baseline in the engagement with behavioural health targets

No significant differences in the engagement with behavioural target were observed according to the level of depressive symptoms at baseline in none of the models tested: unadjusted and adjusted for BMI and prognostic predictors for depression (Table S7, supplementary material).

### 4. Discussion

This secondary analysis of a hybrid effectiveness implementation cluster randomized trial (EIRA study) involving 2531 non-depressed PHC attenders showed that the MHBC intervention was not effective in preventing depression at 12-month follow-up in primary care attenders aged 45–75 years.

To our knowledge, this is the first randomized controlled trial evaluating the effectiveness of a MHBC intervention for the primary prevention of depression in PHC patients exhibiting more than one unhealthy behaviour. Despite the EIRA study is based on a flexible patient-centered approach that was adapted to different PHC settings, significant effects were only observed in two or three behaviours, in any behaviour and in adherence to the Mediterranean diet. We have to note...
that the intervention could not elicitate significant positive changes in physical activity and smoking behaviour. This could be explained by low adherence to the intervention [36]. The average number of individual sessions, which ranged 0–9, was 1.24, and the percentage of participants referred to group sessions and community activities was low. A previous systematic review revealed that the main barriers to adhering to health behaviour change interventions were lack of time, poor motivation, physical limitations and negative thoughts, among other factors [61]. In addition, previous studies have found that patients usually take a passive role during health behaviour PHC consultations [62]. Thus, these aspects might explain why most of the patients initiated an individual intervention, with no positive effects on physical activity and smoking status at 12-month follow-up. Regarding PHC professionals, they received training in motivational interviewing techniques prior to initiation of the intervention. Training was aimed at encouraging PHC professionals to adopt a perspective focused on patient's interests and motivations. However, previous studies have shown that PHC professionals have difficulty in putting motivational interviewing into practice and adopt a paternalistic approach far from a patient-centered perspective [62]. In our study, no assessment was made of PHC professionals' adherence to motivational interviewing techniques, so we do not know if the relatively low positive change of healthy behaviours is only attributable to patient's adherence to the planned MHBC intervention and/or level of motivational interviewing skills of PHC professionals.

Regarding the effectiveness of MHBC interventions in preventing depression, no significant differences were observed between the intervention and the control group in the cumulative incidence of onset of major depression at 12 months and in the reduction of depressive symptoms. We found that the preventive effect of the intervention was not moderated by the symptoms of depression at baseline. Previous studies conducted in the PHC setting found heterogeneous results. For example, Brotons et al., [33] and Siddiqui et al., [35] found that MHBC intervention reduced depressive symptoms in patients with cardiovascular disease [33] or at increased risk for type 2 diabetes [35]. Conversely, Davies, et al., [34] found no effect of a MHBC intervention in patients with pre-diabetes. Similar studies implemented in other settings such as the hospital [63] and the Internet [64,65] did not demonstrate any effect of MHBC interventions on depression. It is worthy of note that none of these previous studies excluded patients with major depression at baseline, so they are not fully comparable to our study. Evidence from previous systematic reviews and meta-analyses of MHBC interventions is inconsistent as well. While a study demonstrated that MHBC interventions improved depressive symptoms in at-risk patients or patients with type 2 diabetes [29], a recent study showed that MHBC interventions reduced depressive symptoms but the effect disappeared when only studies with low risk of bias were included [11]. Again, we must note that none of these previous systematic reviews and meta-analyses excluded patients with major depression at baseline, so they are not fully comparable to our study. In our study, adherence to the planned intervention might explain these results. According to NICE, [66], positive change is more effective when behavioural change is promoted at individual, community and group level. Our intervention included these components, however, group and community activities had a low use [36]. In the present study, we also found that were not significant differences in the engagement with behavioural target based on the level of depressive symptoms at baseline. Additionally, achieving more positive behaviours changes seems not to be related with greater prevention of the onset of major depression at follow-up or with lower symptoms of depression at follow-up.

Our study had several strengths, which increase its value and relevance. Patients with major depression at baseline as confirmed on CIDI were discarded at baseline. Thus, this study is focused on primary prevention of depression. Depression has been evaluated using CIDI and PHQ-9 at baseline and during follow-up. The use of CIDI to evaluate major depression may minimize the risk of classification bias. The intervention was focused on PHC patients with a co-existing profile of unhealthy behaviours, which are highly prevalent in the adult population. Previous studies observed that around 30–40% of the adult population engage in two unhealthy behaviours [18,20,22]. This study included a large sample of patients and PHC centers with different characteristics from different provinces in Spain; therefore, its external validity was relatively optimal. Last but not least, the EIRA study was designed according to the Medical Research Council's evaluation framework [67] and it has used theoretical frameworks to determine the design, data collection, analyses, interpretation, and evaluation of the study.

Despite these strengths, our study presents some limitations. First, the number of participants with positive changes in adherence to a Mediterranean diet, physical activity and smoking cessation and the number of patients who were referred to community activities and group sessions was low. Thus, these intervention factors may result in reduced effectiveness of the intervention in promoting behavioural changes and preventing depression. Second, a considerable number of participants (47 (22.17%) were lost to follow-up. This number was balanced between intervention and control groups; however, it does not rule out attrition biases. In any case, by using multiple imputations for missing outcome data, attrition biases were minimized. Third, the self-exclusion of 3 PHC centers and 387 patients due to failure to use the CIDI possibly introduced selection bias. To minimize confounding biases, the only imbalanced variable, BMI, was included in the analysis; while the adjustment for depressive symptoms at baseline was decided a priori, regardless of whether they were balanced or not, since these have a prognostic value regarding the onset of new episodes of depression. In addition, other prognostic predictors for depression were also included in the analysis. Fourth, participants and PHC professionals were aware of study allocation. These aspects could have resulted in performance and detection bias. However, to reduce bias, it was measured at baseline and follow-up by external evaluators not involved in the implementation of the intervention. Fifth, although adherence to the intervention protocol was assessed, it was measured by taking into account the fidelity of PHC professionals to the planned intervention instead of professionals' skills to carry it out, which might have resulted in an underestimation of the actual fidelity to the protocol [36].

5. Conclusion

The MHBC intervention was not effective in preventing the onset of episodes of major depression and in reducing depressive symptoms in PHC. There is not enough evidence about the use of MHBC interventions for the prevention of major depressive disorder in PHC attenders. More studies are needed to draw robust conclusions. Future studies are needed to assess adherence and fidelity of PHC professionals to the planned intervention through the use of direct measures such as professional's skills to implement the intervention.

Ethical approval

This study was approved by the Research Ethics Committee of the IDIAP Jordi Gol (reference number P16/025) and the local ethics committees of each participating Autonomous Communities.

Analysis code

Can be found in the supplementary material.

Financial support

This study was supported by the Carlos III Health Institute, the Spanish Ministry of Economy and Competitiveness via a health research grant (PI15/00114, PI15/00565, PI15/00762, PI15/01072, PI15/00896, PI15/01412, PI15/01151, PI15/00519, PI15/01133) through
the Research Network in Preventive Activities and Health Promotion in Primary Care (redApp), the European Union ERDF funds (European Regional DevelopmentFund). The project also received a research grant from Carlos III Institute of Health, Ministry of Science and Innovation (Spain) co-funded with European Union – NextGenerationEU funds, through the Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS), with references RD21/0016/0012, RD21/0016/0029, RD21/0016/0005, RD21/0016/0009, RD21/0016/0005 and RD21/0016/0001.

CRediT authorship contribution statement

Irene Gómez-Gómez: Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Emma Motrico: Conceptualization, Investigation, Funding acquisition, Writing – review & editing. Patricia Moreno-Peral: Investigation, Writing – review & editing. Marc Casqujana-Closas: Investigation, Project administration, Data curation, Writing – review & editing. Edurne Zabaleta-del-Olmo: Investigation, Project administration, Writing – review & editing. Ana Claveria: Investigation, Funding acquisition, Writing – review & editing. Joan Llobera: Investigation, Funding acquisition, Writing – review & editing. Ruth Martí-Lluch: Investigation, Writing – review & editing. Rafel Ramos: Investigation, Writing – review & editing. Jose Ángel Madero-Muñoz: Investigation, Funding acquisition, Writing – review & editing. Caterine Vences: Investigation, Writing – review & editing. Marta Domínguez-Garcia: Writing – review & editing. Cruz Bartolomé-Moreno: Writing – review & editing. Jose I. Recio-Rodríguez: Investigation, Writing – review & editing. Juan A. Bellón: Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare they have no conflicts of interest.

Data availability

Data will be made available on request.

Acknowledgements

We would like to thank workers and patients of the PHC centres and their organizations for participating in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2023.02.004.

References
