Online Supplementary text

Methods

Study sample

Participants were excluded when they lacked fluency in Dutch or when they had a primary clinical diagnosis of a psychiatric disorder not subject of NESDA which will largely affect course trajectory: psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder. Data collection included an extensive interview, blood collection, medical assessments and self-reported questionnaires. NESDA was approved by the Medical Ethical Committee of all participating universities and all participants provided written informed consent after all procedures were fully explained. For the current study, we selected 1,115 persons with current (6-month recency) MDD, 513 persons with remitted MDD (presence of a lifetime MDD diagnosis but without an MDD diagnosis or anxiety disorder in the past 6 months), and 652 healthy controls (no lifetime depressive and anxiety disorder) at baseline, assessed using the DSM-IV-based Composite International Diagnostic Interview (CIDI, version 2.1) [1]. Of these 2,080 eligible persons, 214 (9.4%) did not have any follow-up data, leaving a total of 2066 persons eligible for analyses: 968 current MDD persons, 482 remitted MDD persons and 616 controls (N=2,066). Attrition was slightly higher among specialized than in primary care and community (14.2% vs. 8.8% and 4.2%, respectively, $p<0.001$). Of the total sample (N=2,066), 13 persons died during follow-up: 6 persons died by the 4-year follow-up and 7 persons died by the 6-year follow-up, and they were handled as missing persons at that follow-up time point.

Somatic diseases

Previous research within the same cohort found that the used classification of self-reported somatic diseases substantially overlapped with a more stringent classification of somatic diseases, requiring confirmation by medication use (based on drug container inspection) [2,3]. For example, a large majority (88.3%) of the 213 persons reporting cardiometabolic diseases under the less stringent definition, also met the more stringent medication-confirmed definition [2], indicating that the self-report somatic disease classification is valid [2,3]. Sensitivity analyses were performed in the current sample with the more stringent somatic disease classification to see whether results were comparable with those of the less stringent classification. See online Supplement Table S2 for a more detailed description on the definition and classification of somatic diseases.

Major depression characteristics

The Inventory of Depressive Symptomatology (IDS) [4] assesses all DSM-IV criterion symptom domains of MDD, plus commonly associated symptoms and symptoms relevant to melancholic and atypical features. For *overall depression severity,* the total IDS score (range, 0-84) was used, with a higher score indicating a higher severity. The individual depressive 'diurnal variation' item was transformed into a dichotomous variable so that diurnal variation in the morning (yes/no) was indicated [5]. *Depressive symptom clusters* were created by classifying the 30 individual IDS items into a mood, cognitive and somatic/vegetative cluster as used by Schaakxs and colleagues, that were based on previous factor-analytic symptom clusters [5]. Sum scores were created of the included dichotomized mood (10 items; range, 0-10), cognitive (4 items; range, 0-4) and somatic/vegetative IDS symptoms (16 items; range, 0-16) (see online Supplement Table S3 for individual items per cluster).

A measure of the *DSM-5 anxious distress specifier* was previously [6] constructed out of five self-report items from the IDS [4] and the Beck Anxiety Index (BAI) [7] at baseline. Conform to the DSM-5 criterion, anxious distress was present when at least 2 out of the 5 symptoms were endorsed.

Atypical and melancholic depressive subtypes were previously identified using latent class analysis (LCA) based on lifetime CIDI items [8]. The three identified classes were labelled moderate, severe atypical and severe melancholic depression [8], and are also used in this study for consistency. The moderate class was characterized by lower symptom probabilities and lower overall depression severity, whereas the severe atypical and severe melancholic classes were both characterized by higher overall severity [8]. However, the severe atypical and melancholic classes differed in their symptomatology, as the severe atypical class had mainly high probabilities for increased appetite, weight gain and leaden paralysis, while the severe melancholic class was mainly characterized by decreased appetite, weight loss and insomnia [8]. The labels atypical an melancholic do not refer to DSM labels. The atypical and melancholic class differ from the DSM-classification in the number of subtype-specific symptoms for atypical and melancholic depression. Also, the symptom mood reactivity is not a cardinal symptom of the LCA-based atypical subtype. However, the current DSM-definition of atypical depression has been debated [9,10]. Additionally, other LCA studies found comparable symptom patterns with appetite and weight symptoms being the most distinguishing symptoms, underscoring the robustness of the identified subtypes [11,12]. Furthermore, we previously demonstrated that the atypical class was associated with immune-metabolic [13,14] and leptin dysregulations [15], whereas the melancholic class was associated with HPA-axis hyperactivity [13].

Covariates

Covariates were sociodemographic characteristics including *age*, *sex* and *years of education*. Adjustments were additionally made for lifestyle: *smoking status* (never, former, current), *alcohol intake* (<1 drink/week; 1-14/1-21 [female/male] drinks/week; >14/21 [female/male] drinks/week), *physical activity* (International Physical Activity Questionnaire [16], expressed in 1000 metabolic equivalent [MET]-minutes/week), and *body mass index (BMI;* kg/m^2). Past-month *antidepressant use* was assessed based on drug container inspection and classified according to the WHO ATC classification [17]: selective serotonin reuptake inhibitors (SSRI; ATC-code N06AB), tricyclic antidepressants (TCA; ATC-code N06AA) and other antidepressants (Other AD; ATC-codes N06AF/N06AX).

Statistical analyses

Baseline characteristics were compared between current MDD, remitted MDD and healthy control groups, using Chi-square-tests, independent *t*-tests, or Mann-Whitney U-tests where appropriate. Somatic disease incidence variables assessed new onset of somatic diseases at the 2-, 4- and 6-year follow-up assessment, and the time point at which persons reached the first incident somatic disease was assessed as 'time to event'. Persons were censored at the last follow-up assessment when the somatic disease did not occur during follow-up, persons with missing follow-up data were censored at the last follow-up assessment recorded. In a subset-analysis we examined whether current MDD patients with or without anxious distress, LCA-based moderate, atypical and melancholic depressive subtypes differed from controls in 6-year incidence of any somatic disease and somatic disease categories. Cox proportional hazard assumptions were verified by Kaplan-Meier plots and Cox regression analyses with time-dependent variables. Data was statistically analysed using SPSS, version 22 (IBM Corp: Armonk, New York), and all tests were two-tailed with the significance threshold set at 0.05.

Results

Persons with current (n=968) and remitted (n=482) MDD were more often female, had fewer years of education, and had a higher IDS depression score than controls (n=616) (online Supplement Table S4). With regard to lifestyle factors, current and remitted MDD persons were more often current smokers, reported less alcohol intake and had a higher BMI than controls. Persons with remitted MDD had slightly higher physical activity than current MDD persons and controls (online Supplement Table S4).

6-year Incidence of somatic diseases in current and remitted MDD persons versus controls

Incidence rates of self-reported somatic diseases were not substantially different from the rates of medication-confirmed somatic diseases in current and remitted MDD persons versus controls (online Supplement Table S5). The HR estimates for most medication-confirmed somatic disease categories slightly increased when compared to the estimates of self-reported somatic diseases, and *P*-values were also largely comparable (online Supplement Table S5). Additional adjustment for antidepressant use did also not result in major changes of HR estimates and significance. Also, antidepressant use itself was not significantly related to somatic disease incidence in any of the models (data not shown).

Impact of MDD characteristics on 6-year incidence of somatic disease categories

In order to establish causality direction of somatic symptoms (as somatic symptoms may be prodromal symptoms of an underlying developing somatic disease, causing depression), we repeated the any somatic disease incidence analysis in persons who were initially free of any somatic disease at baseline and excluded those who developed any somatic disease in the first two years in follow-up (remaining n=1,144). These analyses revealed a comparable risk (current MDD HR=1.42 and remitted MDD HR=1.12), indicating that the found associations with somatic symptoms are not likely the result of reversed causality.

In post-hoc analyses in the entire sample (N=2,066), we examined the impact of depression characteristics on incidence rate of the four somatic disease categories that were (marginally) significantly linked to current MDD (cardiometabolic, musculoskeletal, digestive diseases, respiratory diseases)(online Supplement Figure S1). For all four somatic categories, again, mainly mood and somatic/vegetative symptom clusters and the majority of individual symptoms were associated with higher incidence (online Supplement Figure S1). The symptom 'decrease in appetite' was associated with higher incidence of respiratory disease, although the 95% confidence interval was very large, suggesting that this may not be a very robust finding. For the musculoskeletal category the two

cognitive symptoms 'future pessimism' and 'self-criticism or blame' were associated with a higher onset risk, and for the digestive category the two cognitive symptoms 'future pessimism' and 'concentration/decision making' were associated with a higher onset risk. These cognitive symptoms were not found for the overall any somatic disease outcome. Overall, these analyses indicate that the depressive symptom domains that were associated with a higher incidence of any somatic disease were also consistently associated with higher incidence of the various specific somatic diseases.

Impact of MDD subtypes on 6-year incidence of any somatic disease and somatic disease categories

There was no significant difference in 6-year incidence rates of somatic diseases between current MDD patients with and without anxious distress versus controls, after adjustment (online Supplemental Table S7). Both the group of MDD persons with and the group without anxious distress had comparable, significantly increased incidence risks than controls for any somatic disease (marginally significant for those with anxious distress) cardiometabolic, musculoskeletal, and gastrointestinal diseases. We have also formally tested this, which confirmed that there was no significant difference between MDD persons with versus without anxious distress (data not further shown). Similarly, LCA-based severe atypical and severe melancholic subtypes versus controls were both significantly associated with a higher incidence of any somatic disease, cardiometabolic, musculoskeletal and gastrointestinal diseases (marginally significant for LCA-based atypical subtype), although the severe melancholic subtype showed somewhat higher HR estimates than the severe atypical subtype. Also, these findings were confirmed when we formally tested this for MDD persons with and without atypical or melancholic features (data not further shown). The LCA-based melancholic subtype significantly predicted an increased onset of respiratory diseases with a relatively large HR estimate compared to controls (HR=3.06, 95%CI=1.59-5.87). The LCA-based moderate class versus controls, only significantly predicted a higher incidence of musculoskeletal and gastrointestinal diseases (online Supplemental Table S7).

Discussion

The finding of marginally increased incidence of respiratory disease in current MDD persons versus controls is in contrast with one study showing that major depression was significantly associated with a higher incidence of asthma and chronic bronchitis or emphysema, but extensive correction for lifestyle was not performed [18]. However, since incident cases with respiratory diseases were the lowest of all somatic disease categories, we cannot rule out potential power issues. Current MDD persons also did not have a higher 6-year cancer incidence than controls. Literature is still inconsistent whether depression increases cancer incidence. One meta-analysis found that depressive symptoms increases cancer onset risks [19], whereas another meta-analysis [20] and other recent studies [21,22] found no association between depression and higher cancer incidence risks. Our study supports the latter findings.

Possibly, some of the somatic/vegetative symptoms may be prodromal symptoms of a somatic disease instead of actual depressive symptoms, which may lead to an overestimation of the found association between somatic/vegetative symptoms and somatic disease incidence. Nevertheless, a study conducted in the same cohort showed that MDD was strongly associated with somatic symptom clusters independent of sociodemographics, lifestyle and presence of somatic diseases under treatment [23], suggesting that somatic symptoms may not be fully explained by somatic diseases.

Generally, depressive subtypes showed comparable increased incidence risks for somatic disease categories as compared to controls, indicating no specificity of subtypes for specific disease categories, except for the melancholic subtype that was associated with a higher incidence risk of respiratory diseases. This is surprising as different depressive subtypes are linked to different biological dysregulations and may therefore be at risk for development of different somatic diseases. For example, atypical depression is associated with leptin dysregulations [15] and obesity [15,24], which possibly may contribute to developments of metabolic diseases. Another study showed that only atypical depression was prospectively associated with a higher incidence of metabolic syndrome and other cardiometabolic risk factors [25]. We however, found that both the LCA-based melancholic and atypical depressive subtypes were associated with an increased incidence of cardiometabolic diseases. This could be because different biological dysregulations may all contribute to the onset of somatic diseases, but through a different pathway [26]. One exception is that only the LCA-based melancholic subtype showed a higher incidence of respiratory diseases versus controls. This may be driven by the specific symptom ‘decrease in appetite’ as it was associated with higher incidence of respiratory disease, although the 95% confidence interval was very large suggesting that this may not

be a very robust finding. It may also be possible that these findings are due to multiple testing and thereby the increased risk of type I errors. Smoking may be a driving factor for this association, although the model was adjusted for smoking status. However, correction for multiple testing would be too strict as the analysed measures are highly correlated and are largely covering one central concept. Interpretation of the results was therefore not based on single tests and P-values, but interpretation was rather based on patterns of the results. MDD persons with and without anxious distress showed no difference in their somatic disease onset risks versus controls. This is inconsistent with one study that found an increased CVD onset risk for MDD patients with mild anxious distress, although lifestyle adjustment was not conducted [27].

This study has important strengths. This study examined whether depression increases the 6-year onset risks of a wide range of common somatic diseases in a large sample of initially somatic disease-free current and remitted MDD persons and controls simultaneously, combining five important main categories of somatic diseases that substantially contribute to a greater disease burden. This is the first study, to our knowledge, that provides insight into the impact of MDD on somatic disease developments and taking the contribution of important clinical depression characteristics into account: depression severity, depressive symptom clusters, individual depressive symptoms and relevant depressive subtypes. Finally, we adjusted for a wide range of important lifestyle factors, and also confirmed that our results were not affected by antidepressant use. Several limitations should be noted. The development of somatic diseases was based on self-report instead of clinician-based assessment. However, in line with previous studies [2,3], results were comparable with those of a more stringent classification of medication-confirmed somatic diseases indicating that our analyses are not due to self-report bias. Also, self-report of somatic diseases corresponded with diagnoses made by general practitioners [2,28], further supporting that self-report classification is a reliable method. As the study focus is on the new onset of various somatic disease categories, these were analyzed as independent outcomes which may have led to possible cross-sectional and longitudinal associations among the somatic disease categories. However, different somatic disease categories generally have different risk factors and pathophysiological mechanisms and the multiple somatic diseases that are closely related were already clustered into these categories, reducing the possibility of associations between the somatic disease categories. As we have no data on the causality of death, we could not determine whether persons died from the target somatic disease and were thus not included as an incident case when they did not report incidence of the target somatic disease before they died. However, the number of deceased persons at follow-up was relatively low in our sample.

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Online Supplementary Tables and Figure

Online supplement Table S1. Adjusted hazard ratios for 6-year incidence of somatic diseases in persons with current and remitted MDD versus healthy controls who were initially free of the somatic diseases under study.

6-year incidence of somatic diseases	Healthy controls N=616	Remitted MDD N=482	Remitted MDD vs. healthy controls (Ref)		Current MDD N=968	Current MDD vs. healthy controls (Ref)	
	N_{disf} (‰)	N_{disf} (‰)	HR	(95%CI)[a]	N_{disf} (‰)	HR	(95%CI)[a]
Any somatic disease	422 (23.0)	316 (30.4)	1.23	(0.92-1.63)	589 (30.2)	1.37	(1.06-1.77)*
Categories							
Cardiometabolic	519 (7.7)	408 (9.1)	1.04	(0.66-1.63)	819 (11.8)	1.78	(1.21-2.60)**
Respiratory	574 (3.3)	450 (5.6)	1.61	(0.88-2.95)	870 (5.6)	1.63	(0.95-2.80)
Musculoskeletal	566 (8.3)	428 (10.5)	1.09	(0.72-1.64)	865 (13.9)	1.74	(1.23-2.47)**
Digestive	599 (6.0)	446 (9.9)	1.50	(0.96-2.33)	854 (11.0)	1.78	(1.20-2.64)**
Cancer	577 (6.8)	440 (7.3)	0.93	(0.58-1.49)	900 (7.0)	1.07	(0.71-1.61)

Abbreviations: MDD, Major Depressive Disorder.

[a] Based on Cox regression analyses. Adjusted for sociodemographics (age, sex, education) and lifestyle (smoking status, alcohol intake, physical activity and body mass index).

N_{disf}= Persons who were initially free of the somatic diseases under study at baseline. ‰=Percentage of persons with an incident somatic disease over 6-year follow-up.

Symbol: * Statistically significant at *P*<0.05, ** Statistically significant at *P*<0.01.

Online Supplement Table S2. Classification of somatic diseases.

Somatic diseases	Somatic disease specific types[a]	Medication confirmation by ATC-codes[b]
Categories		
Cardiometabolic	Hypertension Myocardial infarct Angina pectoris: self-reported condition Cardiac arrhythmia Heart failure status after heart surgery (i.e. heart valve, bypass, balloon treatment, pacemaker) Stroke Diabetes Mellitus type 2 Other heart condition (i.e. heart murmur, artery stenosis, valvular insufficiency/stenosis, other coronary diseases/ cardiovascular abnormalities)	Antihypertensive medication [C02], diuretics [C03], beta blocking agents [C07], calcium channel blockers [C08], agents acting on renin-angiotensin system [C09], beta blocking agents [C07], nitrate vasodilators [C01DA], calcium channel blockers [C08], anticoagulant/antiplatelet agents (antithrombotic agents [B01], acetylsalicylic acid [N02BA01; ≥50% use of ≤100 mg], carbasalate calcium [N02BA15]), lipid modifying agents [C10], digoxine [C01AA05] (frequency daily: >50% of the time), medication used in diabetes [A10].
Respiratory	Asthma Chronic bronchitis Pulmonary emphysema	Medication for obstructive airway diseases [R03], corticosteroids for systemic use [H02], short-acting betasympathomimetics salbutamol [R03AC02] and terbutaline [R03AC03] (when necessary or more often).
Musculoskeletal	Osteoarthritis Rheumatoid arthritis Systemic lupus erythematodes Fibromyalgia	Anti-inflammatory and antirheumatic products [M01; NSAID's], other analgesics and antipyretics [N02B; paracetamol [N02BE03]], corticosteroids for systemic use [H02], immunosuppressants [L04], corticosteroids for systemic use [H02], aminosalicylic acid and similar agents [A07EC] (frequency daily: >50% of the time), folic acid analogues [L01BA] (frequency intravenous per 2 weeks: <50% of the time), aminoquinolines [P01BA] (frequency daily: >50% of the time), opioids [N02A], other analgesics and antipyretics [N02B].
Digestive	Ulcer Irritable bowel syndrome Crohn's disease Colitis ulcerosa Diverticulitis Liver cirrhosis Hepatitis Constipation	Medication for acid-related disorders [A02], laxatives [A06], medication for functional gastrointestinal disorders: spasmolyticum [A03], antidiarrheals, intestinal antiinflammatory/antiinfective agents [A07], corticosteroids for systemic use [H02], immunosuppressants [L04], other analgesics and antipyretics [N02B; paracetamol [N02BE03], bile and liver therapy [A05], antivirals for systemic use [J05], Interferons [L03AB], Laxatives [A06].
Cancer	throat, thyroid, lymphoid, lung, esophagus, bowel, stomach, liver, uterus, cervix, ovary, bladder, testicle, prostate, skin, brain, blood	Medication used in cancer treatment [L01, L02, L03, L04], analgesic medication (opioids [N02A], other analgesics and antipyretics [N02B] and nonsteroidal anti-inflammatory and antirheumatic products [M01A], anti-inflammatory/ antirheumatic agents in combination [M01B].
Any somatic disease		
Any of the five somatic disease categories	First onset of any of the somatic disease specific types out of the five somatic disease categories	Medication confirmation by ATC-codes of any of the somatic disease[b]

[a] Self-reported classification of somatic diseases: Participants were asked: 1) Do you have a diagnosis of 'any of the mentioned somatic disease specific type'? 2) Do you receive medication for this disease? 3) Are you currently under treatment by a physician for this disease?. Somatic diseases were considered present when criterion 1 and at least criterion 2 or 3 were fulfilled.

[b] Medication confirmation was based on past-month medication use registered by drug container inspection and was coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC)-classification system at each assessment [17,29]. Medication-confirmed classification of somatic diseases: self-report somatic diseases confirmed by ATC medication codes. Classification in Supplement Table S3 was used.

Online Supplement Table S3. IDS depressive symptom clusters and individual depressive symptoms.

Depressive symptom cluster	Individual depressive symptoms
Mood symptom cluster	diminished capacity for pleasure
	diminished interest in people/activities
	diminished quality of mood
	diminished reactivity of mood
	feeling anxious or tense
	feeling irritable
	feeling sad
	interpersonal sensitivity
	leaden paralysis
	panic/phobic symptoms
Cognitive symptom cluster	concentration/decision-making problems
	future pessimism
	self-criticism and blame
	suicidal thoughts
Somatic/vegetative symptom cluster	aches and pains
	decrease in appetite
	increase in appetite
	constipation/diarrhea
	diurnal variation with worse mood in morning
	early morning awakening
	low energy level/fatigability
	other bodily symptoms
	problems falling asleep
	problems sleeping
	psychomotor agitation
	psychomotor retardation
	reduced interest in sex
	sleeping too much
	weight loss
	weight gain

Online Supplement Table S4. Baseline characteristics of total sample (N=2,066).

	Current MDD N=968	Remitted MDD N=482	Healthy controls N=616	*P*[a]
Socio-demographic characteristics				
Age, years, mean ± SD	41.2 ± 12.0	44.0 ± 12.61	40.8 ± 14.6	<0.001
Sex, female, n (%)	647 (66.8)	347 (72.0)	374 (60.7)	<0.001
Education, years, mean ± SD	11.7 ± 3.3	12.6 ± 3.2	12.9 ± 3.2	<0.001
Psychiatric characteristics				
Depression severity, IDS score, mean ± SD	32.3 ± 12.2	14.5 ± 9.0	8.4 ± 7.4	<0.001
Antidepressant medication use, n (%)				
Tricyclic antidepressant	39 (4.0)	7 (1.5)	1 (0.2)	<0.001
Selective serotonin re-uptake inhibitor	288 (29.8)	59 (12.2)	4 (0.6)	<0.001
Other antidepressant	107 (11.1)	7 (1.5)	0 (0.0)	<0.001
Any current anxiety disorder, n (%)	619 (63.9)	N/A	N/A	N/A
Number of anxiety disorders, median (IQR)	1.0 (0.0-2.0)	N/A	N/A	N/A
Major depressive subtypes[b], n (%)			N/A	N/A
Anxious distress	500 (52.7)	N/A	N/A	N/A
Moderate	485 (50.1)	N/A	N/A	N/A
Severe atypical	251 (25.9)	N/A	N/A	N/A
Severe melancholic	232 (24.0)	N/A	N/A	N/A
Lifestyle				
Smoking status, n (%)				
never smoker	261 (27.0)	124 (25.7)	230 (37.3)	<0.001
former smoker	285 (29.4)	175 (36.3)	220 (35.7)	
current smoker	422 (43.6)	183 (38.0)	166 (26.9)	
Alcohol intake, n (%)				
< 1 drink a week	376 (38.8)	132 (27.4)	146 (23.7)	<0.001
1-14/1-21 (women/men) drinks a week	556 (57.4)	335 (69.5)	444 (72.1)	
> 14/> 21 (women/men) drinks a week	36 (3.7)	15 (3.1)	26 (4.2)	
Physical activity (1000 MET-min), mean ± SD	3.5 ± 3.1	4.0 ± 3.0	3.8 ± 3.1	0.02
Body Mass Index (kg/m^2), mean ± SD	25.9 ± 5.5	25.8 ± 4.8	25.0 ± 4.6	<0.01
Prevalence of baseline somatic diseases, n (%)				
Any somatic disease	379 (39.2)	166 (34.4)	194 (31.5)	0.01
Cardiometabolic	149 (15.4)	74 (15.4)	97 (15.7)	0.98
Respiratory	98 (10.1)	32 (6.6)	42 (6.8)	0.02
Musculoskeletal	103 (10.6)	54 (11.2)	50 (8.1)	0.16
Digestive	114 (11.8)	36 (7.5)	17 (2.8)	<0.001
Cancer	68 (7.0)	42 (8.7)	39 (6.3)	0.30

Abbreviations: IDS, Inventory of Depressive Symptomatology; MET, metabolic equivalent; MDD, Major Depressive Disorder.

[a] For *P*-value: Analyses of variance were used for continuous variables; Chi-square analyses were used for dichotomous variables.

[b] Depressive subtypes were based on Latent Class Analysis and do not literally resemble DSM-classifications of atypical and melancholic subtypes.

Online Supplement Table S5. Adjusted hazard ratios for 6-year incidence of medication confirmed somatic diseases in persons with current and remitted MDD versus healthy controls who were initially free of the somatic diseases under study.

6-year incidence of somatic diseases	Healthy controls N=616	Remitted MDD N=482	Remitted MDD vs. healthy controls (Ref)		Current MDD N=968	Current MDD vs. healthy controls (Ref)	
	N_{disf} ($\%_i$)	N_{disf} ($\%_i$)	HR	(95%CI)[a]	N_{disf} ($\%_i$)	HR	(95%CI)[a]
Any somatic disease	489 (14.5)	366 (17.5)	1.08	(0.77-1.52)	728 (20.3)	1.45	(1.08-1.95)*
Categories							
Cardiometabolic	524 (7.3)	411 (9.0)	1.10	(0.70-1.73)	831 (11.2)	1.65	(1.12-2.45)*
Respiratory	591 (2.5)	458 (3.1)	1.12	(0.54-2.34)	900 (3.8)	1.40	(0.75-2.62)
Musculoskeletal	597 (5.0)	459 (7.8)	1.35	(0.83-2.19)	927 (9.1)	1.85	(1.20-2.83)**
Digestive	609 (3.0)	462 (4.5)	1.43	(0.76-2.69)	914 (6.7)	2.16	(1.26-3.70)**
Cancer	602 (2.0)	473 (2.5)	1.06	(0.47-2.37)	952 (2.5)	1.31	(0.64-2.67)

Abbreviations: MDD, Major Depressive Disorder.

[a] Based on Cox regression analyses. Adjusted for sociodemographics (age, sex, education) and lifestyle (smoking status, alcohol intake, physical activity and body mass index).

[b] Classification of medication confirmed somatic diseases: self-report somatic diseases that were additionally confirmed by ATC medication codes. See Supplementary Table S1 for a detailed description.

N_{disf}= Persons who were initially free of the somatic diseases under study at baseline. $\%_i$=Percentage of persons with an incident somatic disease over 6-year follow-up.

Symbol: * Statistically significant at $P<0.05$, ** Statistically significant at $P<0.01$.

Online Supplement Table S6. Adjusted hazard ratios for 6-year incidence of any somatic disease by IDS depression severity, symptom clusters and individual symptoms within the total sample that was initially free of any somatic disease (N=1,327).

	6-year incidence of any somatic disease	
	Current MDD, remitted MDD, and healthy controls N=1,327	
	HR	(95% CI)
IDS depression severity		
Total IDS score	1.18	(1.04-1.33)**
IDS depressive symptom clusters		
Mood	1.13	(1.02-1.25)*
Cognitive	1.03	(0.93-1.14)
Somatic/ vegetative	1.18	(1.07-1.31)**
Presence of IDS depressive symptoms		
Problems falling asleep	1.10	(0.87-1.39)
Problems sleeping during the night	1.15	(0.93-1.41)
Early morning awakening	1.03	(0.77-1.38)
Sleeping too much	0.84	(0.54-1.31)
Feeling sad	1.17	(0.91-1.49)
Feeling irritable	1.39	(1.09-1.78)
Feeling anxious or tense	1.24	(0.97-1.58)
Diminished reactivity of mood	0.94	(0.67-1.33)
Diurnal variation (morning)	0.86	(0.56-1.31)
Diminished quality of mood	1.39	(1.10-1.76)**
Decrease in appetite	1.54	(0.98-2.41)
Increase in appetite	0.97	(0.67-1.40)
Weight loss	1.15	(0.84-1.57)
Weight gain	1.06	(0.76-1.48)
Concentration/decision making problems	1.09	(0.83-1.42)
Self-criticism or blame	0.90	(0.69-1.16)
Future pessimism	0.92	(0.66-1.29)
Suicidal thoughts	1.39	(1.02-1.88)*
Diminished interest in people/activities	1.17	(0.84-1.62)
Low energy level/fatigability	1.22	(0.97-1.54)
Diminished capacity for pleasure or enjoyment	0.92	(0.63-1.35)
Reduced interest in sex	0.97	(0.75-1.25)
Psychomotor retardation	1.13	(0.85-1.50)
Psychomotor agitation	1.30	(1.03-1.64)*
Aches and pains	1.81	(1.43-2.30)**
Other bodily symptoms	1.60	(1.21-2.13)**
Panic/phobic symptoms	1.24	(0.94-1.65)
Constipation/diarrhea	1.64	(1.22-2.20)**
Interpersonal sensitivity	1.14	(0.87-1.49)
Leaden paralysis	1.37	(1.10-1.71)**

Abbreviations: IDS, Inventory of Depressive Symptomatology; MDD, Major Depressive Disorder.

[a] Based on Cox regression analyses, adjusted for sociodemographics (age, sex, education) and lifestyle (smoking status, alcohol intake, physical activity and body mass index). Total IDS score and IDS symptom clusters were standardized; IDS items were dichotomized.

Symbol: * Statistically significant at $P<0.05$, ** Statistically significant at $P<0.01$.

Online Supplement Table S7. Adjusted hazard ratios for 6-year incidence of somatic diseases in current MDD persons with depressive subtypes versus healthy controls who were initially free of the somatic diseases under study.

6-year incidence of somatic diseases	Current MDD with anxious distress specifier vs. healthy controls (Ref)		Current MDD without anxious distress specifier vs. healthy controls (Ref)		Current MDD with moderate subtype[b] vs. healthy controls (Ref)		Current MDD severe atypical subtype[b] vs. healthy controls (Ref)		Current MDD severe melancholic subtype[b] vs. healthy controls (Ref)	
	HR	**(95%CI)**	**HR**	**(95%CI)**	**HR**	**(95%CI)**	**HR**	**(95%CI)**	**HR**	**(95%CI)**
Any somatic disease	1.33	(0.98-1.80)	1.46	(1.08-1.95)*	1.15	(0.84-1.58)	1.48	(1.05-2.11)*	1.89	(1.33-2.68)**
Categories										
Cardiometabolic	1.81	(1.17-2.79)**	1.80	(1.16-2.80)**	1.52	(0.97-2.39)	1.94	(1.19-3.16)**	2.29	(1.36-3.86)**
Respiratory	1.60	(0.87-2.96)	1.66	(0.89-3.09)	0.96	(0.48-1.94)	1.72	(0.85-3.51)	3.06	(1.59-5.87)**
Musculoskeletal	1.71	(1.15-2.53)**	1.77	(1.19-2.63)**	1.53	(1.02-2.29)*	1.81	(1.15-2.84)*	2.24	(1.41-3.56)**
Digestive	1.78	(1.14-2.77)*	1.69	(1.07-2.66)*	1.65	(1.05-2.57)*	1.62	(0.95-2.75)	1.94	(1.14-3.31)*
Cancer	1.07	(0.66-1.74)	1.04	(0.63-1.69)	1.02	(0.63-1.66)	1.21	(0.67-2.19)	1.15	(0.63-2.09)

Abbreviations: MDD, Major Depressive Disorder.

[a] Based on Cox regression analyses. Adjusted for sociodemographics (age, sex, education), and lifestyle (smoking status, alcohol intake, physical activity and body mass index).

[b] Depressive subtypes were based on Latent Class Analysis and do not literally resemble DSM-classifications of atypical and melancholic subtypes.

N_{disf}= Persons who were initially free of the somatic diseases under study at baseline. **%**$_i$= percentage of persons with an incident somatic disease over 6-year follow-up.

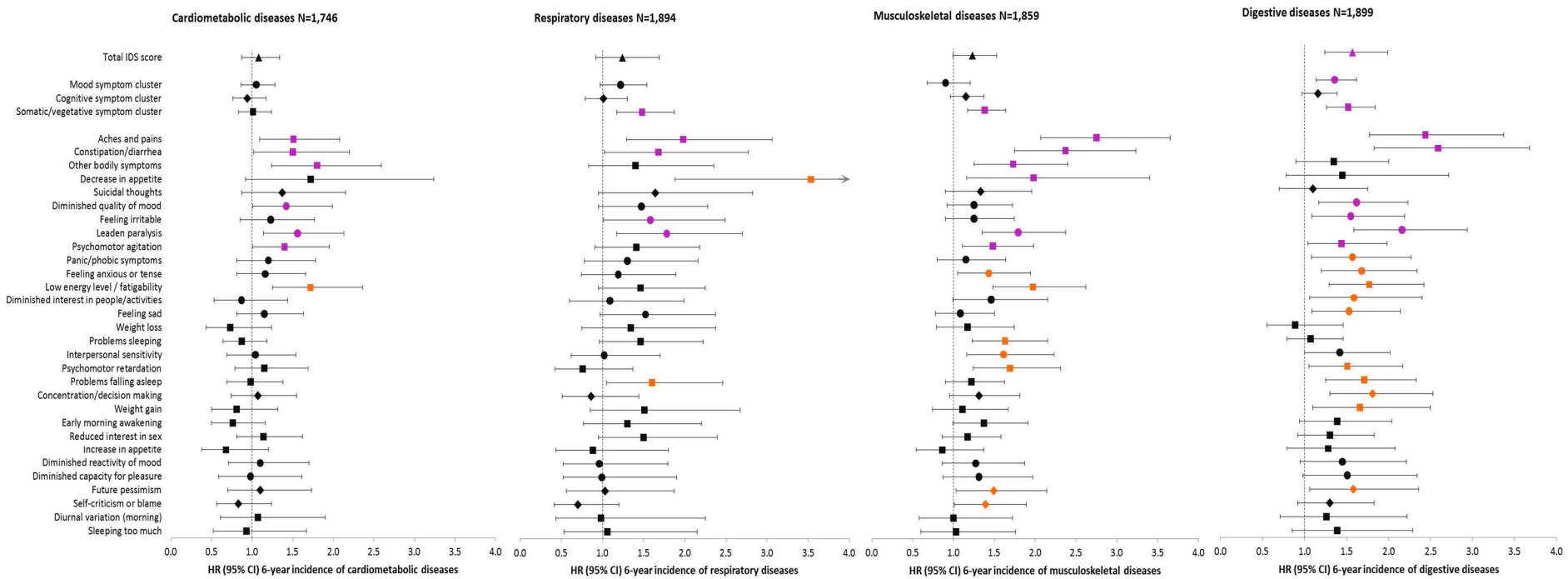
Symbol: * Statistically significant at *P*<0.05, ** Statistically significant at *P*<0.01.

Online Supplement Table S8. Percentage per depressive subtype of persons with 6-year incident somatic diseases of those who were initially free of the somatic diseases under study.

6-year incidence of somatic diseases	Current MDD				
	with anxious distress N=500	without anxious distress N=449	Moderate subtype[a] N=485	Severe atypical subtype[a] N=251	Severe melancholic subtype[a] N=232
	N_{disf} ($\%_i$)	N_{disf} ($\%_i$)	N_{disf} ($\%_i$)	N_{disf} ($\%_i$)	N_{disf} ($\%_i$)
Any somatic disease	293 (30.0)	284 (30.6)	296 (2.4)	150 (54)	143 (37.1)
Categories					
Cardiometabolic	417 (12.5)	384 (11.2)	407 (9.6)	211 (15.2)	201 (12.9)
Respiratory	447 (5.8)	408 (5.4)	441 (3.2)	220 (6.8)	209 (9.6)
Musculoskeletal	434 (14.3)	414 (13.5)	436 (11.5)	223 (16.6)	206 (16.0)
Digestive	432 (12.0)	404 (10.4)	432 (10.2)	222 (11.7)	200 (12.0)
Cancer	461 (6.9)	422 (6.6)	454 (6.6)	231 (7.4)	215 (7.4)

Abbreviations: MDD, Major Depressive Disorder.

N_{disf}= Persons who were initially free of the somatic diseases under study at baseline. $\%_i$= percentage of persons with an incident somatic disease over 6-year follow-up. [a] Depressive subtypes were based on Latent Class Analysis and do not literally resemble DSM-classifications of atypical and melancholic subtypes.



Online Supplement Figure S1. Adjusted hazard ratios for 6-year incidence of somatic disease categories by IDS depression severity, symptom clusters and individual IDS symptoms within the total sample that was initially free of the somatic diseases under study.

Footnote online Supplement Figure S1: Abbreviations: BMI, Body Mass Index; CI, confidence interval; IDS, Inventory of Depressive Symptomatology; HR, hazard ratio; MDD, Major Depressive Disorder.

Based on Cox regression analyses. Analyses were adjusted for sociodemographics (age, sex, education) and lifestyle (smoking status, alcohol intake, physical activity, BMI). Total IDS score and IDS symptom clusters were standardized; IDS items were dichotomized. Error bars represent 95% CI's. Purple estimates are significant for specific somatic disease categories and for any somatic disease(P<0.05) (Figure 1). Orange estimates are only significant for specific somatic disease categories (P<0.05).