

1 **Association of physical frailty with cognitive function and mood in older adults**
2 **without dementia and depression**

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9
10 **Abstract**

11 **Background/aim:** Physical frailty is thought to be related with a decline in cognitive
12 function, mood, and social activities, especially in patients with depression and dementia.
13 It is not clear whether or not physical frailty is associated with an impairment in cognitive
14 function and mood in patients without dementia and depression. In this study, we
15 evaluated the association of physical frailty with cognitive function and mood in geriatric
16 patients without dementia and depression.

17 **Material and Methods:** In this study, 612 patients aged 65 years and over were
18 evaluated. Physical frailty was assessed by using Fried criteria. Furthermore,
19 comprehensive geriatric assessment was performed to each patient.

20 **Results:** Median age of the patients was 72 years (min-max: 65-93), 58% were female,
21 and 6.5% were frail. Clock drawing ($p<0.001$), MMSE ($p<0.001$), and Yesevage Geriatric
22 Depression Scale ($p:0.010$) test results were worse in frail patients compared to pre-frail
23 and robust ones. Age ($p:0.009$), being university graduate ($p:0.031$), three words recall

1 test (p:0.014), Activities of Daily Living (ADL) (p:0.006), Instrumental Activities of
2 Daily Living (IADL) (p<0.001), and MNA-SF (p:0.001) scores were determined to be
3 independent related factors of frailty.

4 **Conclusion:** We have demonstrated that cognitive function and mood might be
5 associated with physical frailty in patients without dementia and depression.

6 **Key words:** Frailty, cognitive function, mood, dementia, depression
7

8 **1. Introduction**

9 Frailty is common in older age and predicts high risk for health-related problems,
10 including institutionalization, mortality, falls, and hospitalization with consequent
11 negative influences on the quality of life [1-3]. It is a condition caused by a decrease in
12 reserve capacity in systems such as brain, immune system, endocrine, and skeletal muscle
13 in older adults [4-6]. Individuals in the same chronological age may be very different in
14 terms of health and functional status. The concept of frailty has been developed to explain
15 this heterogeneity among older adults [7]. The main and the best known conceptualization
16 of physical frailty is the one suggested by Fried et al, who defined frailty as a biological
17 syndrome resulting from the cumulative decline of different physiological systems. [4].

18 Cognitive impairment indicates reduction in intellectual functions, which ranges
19 from forgetfulness to dementia. The association between frailty and cognition has been
20 mentioned in recent studies. In the study by Avila-Funes et al, patients were divided into
21 two groups as robust and frail. The prevalence of cognitive impairment was higher in the
22 frail group (frail group 22%, robust group 10%), however, patients with dementia and
23 depression were included in this study [1]. Samper-Ternent et al. examined patients with
24 Mini-Mental State Examination (MMSE) score after grouping as frail and robust. At the

1 end of the 10 year follow up, cognitive decline was found to be greater in the frail group
2 than in the robust group [8].

3 Depression is not a normal consequence of aging. Loss of function or
4 independence, persistent bereavement, and serious depression are pathological and
5 should be treated. Untreated depression causes important health problems such as
6 complicated chronic conditions including heart disease, diabetes, hypertension, and
7 stroke. It also increases health care costs [9-11]. Not only depressive disorder, but also
8 depressive symptoms have high influence on sense of well-being, disability, and
9 utilization of health care services in older adults [12-14]. The relationship between frailty
10 and depression has been examined in the literature, but no consensus has been reached.
11 In a review, it was reported that the high percentage of frail older adults have depressive
12 symptoms. It is assumed that similar mechanisms play role in depression and frailty, but
13 these information are insufficient to explain the relationship [15].

14 We have hypothesized that there may be a vicious cycle between physical frailty,
15 cognitive function and mood in geriatric patients independent from dementia and
16 depression. Therefore, the purpose of the present study is to evaluate the relationship
17 between physical frailty, cognitive function and mood in patients without dementia and
18 depression in community dwelling older persons.

19 **2. Material and Methods**

20 **2.1. Participants**

21 The study was designed as cross-sectional study. Patients admitted between June
22 2014 and September 2016 were evaluated. One thousand and fifty patients admitted to
23 geriatric medicine outpatient clinic consecutively were evaluated and 612 were included
24 after applying exclusion criteria. Patients over 65 years of age who could be appraised

1 with the Fried frailty criteria were included in the study. Patients with the following
2 criteria were excluded from the study: 1) MMSE score <20; 2) Yesavage Geriatric
3 Depression Scale (GDS) short form >5; 3) patients with diagnosis of depression and/or
4 dementia; 4) patients with diagnosis of psychiatric disorders including schizophrenia,
5 bipolar disorder, borderline personality disorder, etc.;5) patients using antidepressants,
6 antipsychotics, sleep medications, dementia drugs. Age, sex, smoking status, alcohol
7 consumption, chronic diseases, number of drugs, whom living with (partner, children,
8 alone, etc.), education level, number of falls, fractures in the last year, unintentional
9 weight loss during the last year, and urinary incontinence were recorded. Height (m),
10 weight (kg), calf, and upper-mid arm circumferences were measured for each participant.
11 The patients were weighed in the outpatient clinic after, fasting, wearing light clothes and
12 taking off their shoes and their height was measured with the shoes removed. Body mass
13 index (BMI) was calculated by dividing the patient's weight (kg) by the square of the
14 height (m²).

15 **2.2. Cognitive Function Assessment**

16 Within comprehensive geriatric assessment, cognitive assessment was performed.
17 The cognitive functions of the patients were evaluated by clinical assessment, the MMSE
18 and The Clock Drawing Test (CDT). The MMSE, developed by Folstein in 1975, is
19 thoroughly used to measure cognitive functions. Generally, the MMSE score higher than
20 20 points is thought to indicate good cognitive performance [8]. However, due to different
21 literacy and low educational status rates in different countries, there are different cut-off
22 points indicating poor cognitive performance in the literature [16-19]. In this study, the
23 patients with MMSE \geq 20 points and no diagnosis for dementia were included in the study.
24 Three-word recall was also recorded to evaluate patients' immediate memory.

1 We used the CDT that was initially used by Stahelin et al., Its score ranges from
2 0 to 6 points and the point <4 in CDT was accepted to show low cognitive performance
3 [20-22]. CDT score was examined individually for each patient. It was observed that there
4 was no dementia in patients who got 0 on the test and had a score below 4, and the reason
5 for failure was due to low education level.

6 After cognitive and clinical assessment, patients who met DSM-V criteria for
7 dementia were excluded from the study. Diagnosis of mild cognitive impairment was
8 made according to Petersen criteria.

9 **2.3. Physical Frailty Assessment**

10 An adapted version of the frailty phenotype of Fried et al. was used to detect
11 physically frail older adults [4]. Fried criteria is well-established in the literature and the
12 most frequently used diagnostic criteria [23]. Weight loss, exhaustion, physical activity,
13 walking speed, and grip strength were the parameters that were evaluated in the Fried
14 criteria. According to these criteria, the patients scoring 3 or more were reported as frail,
15 scoring 1 or 2 points as pre-frail, and scoring 0 as robust.

16 With a hand-held dynamometer (Takei A5401), three different grip measurements
17 were made by using both hands and the best was recorded. The devices (scale, handgrip)
18 used in the study were calibrated and used under appropriate conditions. The walking
19 speed of 15 feet for each patient was evaluated by the timed up and go test.

20 **2.4. Psychological Assessment**

21 Depressive symptoms were assessed clinically and by performing Yesavage GDS
22 short form. A score of six or greater is considered clinically significant [24]. The patients
23 having <6 points in this scale and no diagnosis for depression were included for the study.

2.5. Comprehensive Geriatric Assessment Parameters

Basic activities of daily living (ADL) and instrumental activities of daily living (IADL) were performed to measure the functional capacities of the patients. ADL was evaluated using the Katz Scale which assesses the degree of dependence on six basic activities: feeding, sphincter control, transferring, personal hygiene, dressing, and bathing. The subject is classified based on the number of activities on which he/she is dependent to others [25, 26]. The Lawton Brody Scale was used for the evaluation of IADL; this scale assesses eight activities: using a telephone, transportation, shopping, cooking, doing household chores, taking prescribed medications, and financial affairs management [27].

The nutritional status of the patients was appraised with the Mini Nutritional Assessment short form (MNA-sf), where the total score of ≤ 11 was described as the risk of malnutrition [28].

2.6. Ethics

Informed consent forms were received from all participants in the study and the study protocol was evaluated and approved by the ethics committee (GO 15/36-25).

2.7. Statistical analysis

Descriptive statistical results were offer as frequencies and percentage for categorical variables. Continuous variables were tested with histogram and Kolmogorov-Smirnov tests to decide whether or not the parameters had normal distribution. The skewed variables were presented as median (minimum-maximum). Comparisons of categorical variables between groups were performed by Chi-square or Fischer exact tests where appropriate. The skewed variables were compared between two groups with Mann-

1 Whitney U test. Kruskal-Wallis and Jonckheere-Terpstra tests were used for the analyses
2 between three or more groups for those with skew distribution. Binary Logistic
3 Regression analysis was used to determine to independently associated parameters for
4 frailty, and values that showed a significant difference in the univariate analysis results
5 of the frail and non-frail groups and lower than $p < 0.20$ were included in this analysis.
6 Odds Ratios (OR) with a 95% confidence interval (CI) was calculated for each variable.
7 Statistical significance was evaluated as p value lower than 0.05. All statistical results
8 were obtained using the “Statistical Package for Social Sciences” (SPSS) 22.0 version.

9 **3. Results**

10 Six hundred and twelve patients aged 65 years and older, living in the community
11 were included in this study. The median age of patients were 72 years (range 65-93), 58%
12 were female, 19.2% were university graduates, %65.3 were living with their partners or
13 families. The three most common comorbid conditions were hypertension (67.2%),
14 diabetes mellitus (35.9%), and urinary incontinence (33.2%). The frequencies of
15 comorbid diseases and geriatric syndromes are shown in Table 1.

16 Among the 612 older patients evaluated 276 patients (45.1%) were classified as
17 robust, 296 patients (48.4%) were classified as pre-frail, and 40 patients (6.5%) were
18 classified as frail. Pre-frail and frail participants were more likely to be older ($p < 0.001$),
19 less educated ($p: 0.006$), had decreased calf circumference ($p: 0.047$), and increased
20 number of drugs ($p: 0.041$) than robust ones. A significant decrease in weight was
21 observed from the robust to the frail group ($p < 0.001$). In the frail group; the Katz ADL
22 ($p < 0.001$), Lawton Brody IADL ($p < 0.001$), CDT ($p < 0.001$), MMSE score ($p < 0.001$), and

1 MNA-sf ($p < 0.001$) scores were lower and Yesavage GDS score ($p: 0.010$) was higher
2 compared to the non-frail group.

3 Median hand grip strength was 22.8 kg (range 6.7-52.4) and median 15 feet
4 walking time was 4.5 seconds (range 1.5-28.5). Frail group was powerless ($p < 0.001$) and
5 walked slower ($p < 0.001$) compared to the non-frail ones. In Table 1, demographic
6 characteristics, comorbid diseases, and comprehensive geriatric assessment of the
7 patients were given according to the degree of frailty.

8 After logistic regression analyses, age (OR: 1.093, 95% CI: 1.022-1.169, $p: 0.009$),
9 being university graduate (OR: 0.020, 95% CI: 0.001-0.703, $p: 0.031$), ADL (OR: 0.448,
10 95% CI: 0.252-0.796, $p: 0.006$), IADL (OR: 0.760, 95% CI: 0.665-0.869, $p < 0.001$), MNA-
11 sf (OR: 0.721, 95% CI: 0.599-0.869, $p: 0.001$), and three words recall (OR: 0.531, 95%
12 CI: 0.320-0.880, $p: 0.014$) scores were determined to be independent factors related to
13 frailty. The parameters included in the regression analysis were age, weight, congestive
14 heart failure, urinary incontinence, hypertension, hyperlipidemia, history of falls, sleep
15 duration, number of drugs, ADL score, IADL score, CDT score, three words recall, and
16 MNA-sf. The parameters independently associated with frailty are shown in Table 2.

17 **4. Discussion**

18 This study aimed to examine the association between physical frailty, cognitive
19 function, and mood in community-dwelling older patients without dementia and
20 depression. MMSE, CDT, Yesavage GDS, and three words recall tests' results were
21 shown to be worse in frail patients than in non-frail ones in univariate analyses. Moreover,
22 three words recall test was found to be an independent correlate for frailty in regression
23 analysis. This study demonstrated that there is a relationship between physical frailty and
24 cognitive function and mood in older adults regardless of having dementia or depression.

1 The frequency of frailty in patients with depression and dementia has been shown in
2 previous studies. In our study, although the patients with these diagnoses were excluded
3 from the study, it was shown that the scores of the scales assessing cognition and mood
4 were poor in the frail group. By showing these results, this study adds to the existing
5 literature on physical frailty and its relationship with other common syndromes of the
6 older adults.

7 Despite the exclusion of the diagnosis of depression in this study, depressive
8 symptoms detected in Yesavage GDS were found to be increased in the frail group than
9 the non-frail subjects. The bidirectional relationship between mood and frailty has been
10 explored in some studies, but not well documented. Ormeland and colleagues have shown
11 that frailty is a stronger predictor for depressive symptoms [29]. Gayman and colleagues
12 have found that frailty deteriorated depressive symptoms [30]. Similarly, Collord and
13 colleagues have indicated that the severity of frailty has a negative influence on late-onset
14 depressed mood [31]. However, in these studies patients with a diagnosis of depression
15 have not been excluded. In our study, patients with a diagnosis of depression were
16 excluded from the study, and geriatric depression scale scores were found to be higher in
17 the frail group.

18 The review by Mezuk and colleagues described the positive correlation between
19 frailty and depression in detail [32]. The results summarized in this systematic review
20 support the hypothesis that frailty and depression are comorbid geriatric syndromes in a
21 subgroup of older individuals; at the same time, frailty is also a risk factor for the
22 development and persistence of depressive symptoms. The same common symptoms and
23 risk factors may also explain why frailty could sustain depressive symptoms and leads
24 subjects to new symptoms of depression [33]. In the majority of these studies, the

1 diagnosis of dementia and depression was not excluded. In two studies excluding the
2 diagnosis of dementia but not depression, depressive symptoms were associated with
3 frailty, but it was not associated with the pre-frail group and was shown to be weakly
4 related, respectively [34, 35]. So, we can say in the light of our and similar studies that
5 there is a positive correlation between frailty and depressive symptoms irrespective of
6 having diagnosis of depression and dementia. In daily practice, when a geriatric patient
7 with frailty is seen, depressive symptoms should be checked to rule out or early detect the
8 diagnosis of depression. Therefore, the frailty assessment should be routinely involved in
9 the assessment of a geriatric patient.

10 Cognitive impairment was more presumably to be present among pre-frail and
11 frail older persons than their robust peers. This is in compromise with cross-sectional
12 studies which show a higher prevalence of cognitive impairment within physically frail
13 older persons [36-38]. The association between frailty and cognitive impairment is
14 controversial in the literature. Although studies show that frailty may be an indicator of
15 mild cognitive impairment and dementia, there appears to be a correlation between the
16 initiation of frailty and cognitive decline. These two situations may be sharing the same
17 physiopathological mechanisms [1, 39-41]. That's why the assembling of frailty and
18 cognitive impairment can increase an individual's vulnerability and deepen the
19 deterioration in cognitive status [36,37].

20 The connection between frailty and cognitive impairment risk may be accounted
21 by common etiopathogenetic mechanisms. Cognitive decline that frailty contributes may
22 be addressed in many different pathways [39, 42]. Cognitive decline is a course that starts
23 with small changes in a few domains and progresses in many domains slowly. In some
24 dementia types which cortices, the substantia nigra, and the striatum are often changed,

1 accumulation of neural plaques and neurofibrillary tangles is involved in the etiology of
2 the decline. It has been shown in some studies that changes in these regions of the brain
3 are associated with alterations in the components of frailty such as slow gait and weight
4 loss. These findings and the outcomes of our study demonstrate that alteration in the
5 neural system may be predictive for frailty [43-45]. Further studies are needed to explain
6 this precise relationship.

7 Another mechanism that may explain the relationship between cognitive
8 dysfunction and frailty is the inflammatory process. Pro-inflammatory cytokines increase
9 during stress reactions, and interleukin-1 and tumor necrosis factor levels increase in
10 diseases that trigger inflammatory reactions. Interleukin-6 increases with the aging
11 process, and these increased cytokines accelerate the catabolic process resulting in
12 diminished lean body mass and muscle, leading to frailty. Furthermore, peripheral pro-
13 inflammatory cytokines increase the central pro-inflammatory cytokine levels leading to
14 neurotoxicity and cognitive impairment. It is stated that inflammatory reactions
15 contribute to physical frailty and cognitive dysfunction in the direction of this knowledge
16 [46-49].

17 In our study, it was observed that the age of the patients increased with the increase
18 in the degree of frailty. The association of pre-frailty and frailty with age is consistent
19 with the findings of previous studies [50, 51]. Physiological changes in many systems
20 when aging and their consequent interactions with pathological mechanisms make aging
21 a predisposing factor for frailty [6]. According to the results of our study, the relationship
22 between the level of education and frailty was determined with higher frailty prevalence
23 rates among lower educated people. Hoogendijk and colleagues found similar results and
24 concluded in their study that public health strategies about struggling with frailty should

1 also include focusing on patients' education levels. The knowledge regarding high
2 prevalence of frailty in low educational level improved this strategy [52]. Arguments have
3 shown that longtime education in early life may enhance the development of cognitive
4 reserve throughout the life process [53, 54]. All patients underwent comprehensive
5 geriatric assessment in our study and ADL, IADL, and nutritional status were detected to
6 be independently related parameters with frailty. Similarly, some studies in the literature
7 have shown that there is a relationship between frailty and basic activities of daily life
8 and instrumental activities of daily life [6]. We know that frailty has multi-dimensional
9 aspects. Physiologic, cognitive, behavioral and physical reserves of the geriatric patients
10 are negatively affected by frailty. Therefore, all the parameters in comprehensive geriatric
11 assessment may be affected by frailty. In this study, evaluation of patients with good
12 general condition who were admitted to the outpatient clinic was reflected to the results
13 as low prevalence of frailty. It cannot be generalized to the whole geriatric population
14 because of the lack of nursing home residents among the patients enrolled.

15 The major limitation of this study is having a cross-sectional design. We could not
16 determine causality between frailty, cognitive function, and depressive symptoms due to
17 the cross-sectional design of the study. The strengths of our study are excluding patients
18 with depression and dementia and including a large number of patients. The results of this
19 study revealed that frailty is associated with depressive symptoms and cognitive
20 dysfunction even in the patients without depression or dementia diagnosis, in a very large
21 sample. In some studies, in the literature, it was seen that the MMSE score was taken as
22 a cut off 20. In our study, when the patients were examined one by one with their
23 education level, it was decided to determine the MMSE score as 20.

1 In conclusion, the relationship between physical frailty and cognitive function and
2 depressive symptoms was shown in this study. Prevention of frailty and intervention of
3 reversible factors have become important in order to minimize the consequences. There
4 is a need for future work to elucidate this issue clearly. Frailty should be evaluated
5 comprehensively. In patients with physical frailty cognition and mood should always be
6 assessed and precautions should be taken on time. Increasing awareness on all aspects of
7 frailty should be an aim for healthcare policies and further studies showing impact of
8 frailty on healthcare costs will further emphasize its importance.

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29 **Table 1.** Comparison of comprehensive geriatric assessment parameters between groups
 30 determined by the Fried's Frailty Index

	Total (n=612)	Robust (n=276)	Pre-frail (n=296)	Frail (n=40)	P value
Age, year	72 (65-93)	71 (65-88)	72 (65-90)	78 (65-93)	<0.001
Female, %	355 (58)	153 (55.4)	175 (59.1)	27 (67.5)	0.304

Male, %	257 (42)	123 (44.5)	121 (40.9)	13 (32.5)	0.304
Education level, university graduate, %	116 (19.2)	70 (25.4)	44 (14.7)	2 (5)	0.006
Weight, kg	74 (43-145)	76 (45-145)	73 (43-116)	67 (50-98)	<0.001
BMI, kg/m ²	27.6 (17-50.1)	27.8 (18.6-50.1)	27.6 (17-44.3)	26.9 (21-40)	0.431
Calf circumference, cm	36 (17.9-52)	36.7 (17.9-51)	36 (23.5-52)	34.5 (24-46)	0.047
Hypertension, %	411 (67.2)	172 (62.3)	207 (69.9)	32 (80.0)	0.031
Diabetes mellitus, n (%)	220 (35.9)	100 (36.2)	104 (36.2)	16 (40.0)	0.827
Osteoporosis, n (%)	143 (23.4)	61 (22.2)	72 (24.3)	10 (25.0)	0.808
Coronary artery disease, n (%)	91 (14.9)	38 (13.8)	46 (15.5)	7 (17.5)	0.745
Chronic obstructive pulmonary disease, n (%)	34 (5.6)	12 (4.3)	18 (6.1)	4 (10)	0.297
Hyperlipidemia, %	189 (30.9)	94 (34.1)	87 (29.4)	8 (20.0)	0.147
Congestive heart failure, %	21 (3.4)	7 (2.5)	10 (3.4)	4 (10)	0.053
History of falls, %	150 (24.5)	47 (17.0)	89 (30.1)	14 (35)	0.001
Fracture, n (%)	72 (12.1)	29 (10.9)	36 (12.4)	7 (18.4)	0.410
Urinary incontinence, %	203 (33.2)	78 (28.3)	104 (35.1)	21 (52.5)	0.006
Number of drugs	4 (0-17)	3 (0-17)	4 (0-13)	5 (0-10)	0.041
Katz ADL score	6 (0-6)	6 (5-6)	6 (0-6)	5 (0-6)	<0.001
Lawton IADL score	17 (0-17)	17 (7-17)	17 (7-17)	13 (0-17)	<0.001
CDT score	6 (0-6)	6 (0-6)	6 (0-6)	3 (0-6)	<0.001
MMSE score	28 (20-30)	29 (20-30)	28 (20-30)	27 (21-30)	<0.001
Three words recall	3 (0-3)	3 (0-3)	2 (0-3)	2 (0-3)	<0.001
MNA-sf, score	14 (0-14)	14 (2-14)	13 (0-14)	11 (6-14)	<0.001
Yesavage GDS score	0 (0-5)	0 (0-5)	0.5 (0-5)	1 (0-5)	0.010
15 feet walking time, seconds	4.5 (1.5-28.5)	4.03 (1.5-6.7)	4.82 (1.9-25.2)	8.78 (3.9-28.5)	<0.001

Handgrip, kg	22.8 (6.7- 52.4)	27.8 (14.4-52.4)	19.9 (7.7- 48.6)	14.0 (6.7- 31.8)	<0.001
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1 * The skew variables were presented as median (minimum-maximum). Categorical variables were given as numbers and percentages.

2 * BMI: Body Mass Index, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, CDT: Clock Drawing

3 Test, MMSE: Mini-Mental State Examination, MNA-sf: Mini Nutritional Assessment short form, GDS: Geriatric Depression Scale

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22 **Table 2.** Parameters independently associated with frailty

	OR	95% CI	p value
Age	1.093	1.022-1.169	0.009
Educational status, university graduate	0.020	0.001-0.703	0.031

ADL score	0.448	0.252-0.796	0.006
IADL score	0.760	0.665-0.869	<0.001
MNA-sf	0.721	0.599-0.869	0.001
Three words recall	0.531	0.320-0.880	0.014

1 *All the parameters those had p value lower than 0.20 when compared between frail and non-frail patients in univariate
2 analysis were included in regression analysis. The parameters included in the regression analysis were age, weight,
3 congestive heart failure, urinary incontinence, hypertension, hyperlipidemia, history of falls, sleep duration, number of
4 drugs, ADL score, IADL score, Clock drawing test score, three words recall, and Mini-nutritional assessment-SF.
5 Backward elimination method was used for binary logistic regression analysis. The last model (step 13) was presented
6 in this table. This regression model had omnibus test result as chi-square 93,206 and $p < 0.001$. Also, this model had p
7 value as 0.935 for Hosmer-Lemeshow test and Nagelkerke R square was 0.469.

8 * ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, MNA-sf: Mini Nutritional Assessment short form

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