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Mortality Risk Following a Household Suicide

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Abstract

IMPORTANCE The broader mortality risks faced by household members following a suicide remain poorly understood, particularly in low- and middle-income countries.

OBJECTIVES To estimate the risk of all-cause and cause-specific mortality among surviving household members after a suicide within the household and to identify individual and contextual factors associated with mortality risk using data from a national population-based cohort in Brazil.

DESIGN, SETTING, AND PARTICIPANTS This nationwide cohort study used data from the 100 Million Brazilian Cohort linked to the Mortality Information System (SIM) (2001-2018). All individuals who lived in a household with a suicide index case were considered exposed. Data were analyzed from March 2023 to September 2025.

MAIN OUTCOMES AND MEASURES All-cause mortality, cause-specific mortality, and suicide. Outcomes were derived from the national mortality tracking system. The adjusted hazard ratio of all-cause and specific-cause mortality was calculated using a multivariate, time-varying Cox regression. The risk factors associated with increased mortality, including characteristics of the index case, surviving household members, household conditions, and the timing since the suicide event were also analyzed.

RESULTS The cohort included 101 million individuals, of which there were 47 982 suicide index cases identified. Household members exposed to a suicide (11 070 [7%] Black, 82 407 [53%] Parda, and 57 726 [37%] White) had a 32% higher risk of all-cause mortality (adjusted hazard ratio [aHR], 1.32; 95% CI, 1.28-1.36). The risk of suicide among exposed individuals was more than 4 times higher (aHR, 4.42; 95% CI, 3.86-5.07), with 101 of these deaths (44%) occurring within 2 years of the index suicide case. The population attributable fraction for suicide was 77%. Elevated risks were also observed for other external causes (eg, assault and falls) and nonexternal causes (eg, neoplasms and circulatory and respiratory diseases). Mortality risk was highest when the index case was female and younger, among male survivors, and individuals aged 25 to 59 years. Better household conditions were associated with lower risks of both suicide and all-cause mortality.

CONCLUSIONS AND RELEVANCE Exposure to suicide within the household was associated with a substantial increase in both suicide-specific and all-cause mortality among surviving household members, particularly in the immediate aftermath. These findings underscore the urgent need to incorporate targeted postvention strategies into comprehensive suicide prevention efforts.

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Key Points

Question Does household exposure to suicide increase mortality among surviving members, and what risk factors and temporal patterns are involved?

Findings In this cohort study of over 100 million Brazilians, household suicide exposure was associated with a 32% higher risk of all-cause mortality and a 4-fold higher risk of suicide, with over half of suicides occurred within 2 years following the index case. Risks were greatest when the index cases were young or female and among those in poor housing conditions.

Meaning These findings suggest that household suicide exposure confers substantial time-sensitive mortality risks, underscoring the need for targeted early postvention strategies.

+ Supplemental content

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Introduction

Suicide is a major global public health issue with profound impacts that extend beyond the deceased to surviving family members.[1-4] The psychological, social, and economic consequences of suicide ripple through families and communities.[2-4] Surviving family members are frequently confronted with a complex mix of grief, stigma, and structural vulnerability[5-7] that adversely affects their mental[8-11] and physical well-being.[9] These challenges are heightened in low-income settings, where the burden of suicide intersects with barriers to mental health care, socioeconomic hardship, and cultural stigma.[12,13]

Research has largely focused on suicide risk among bereaved relatives,[2,14-25] though less is known about how many people are exposed and need support in the broader household[19] or about their overall mortality risk from nonsuicide causes.[9,26-28] Prior studies have lacked unexposed comparison groups, reducing causal inference and limiting the ability to attribute observed outcomes to suicide exposure. Furthermore, there is a need to consider when excess mortality arises and how it varies over time following a suicide in the household. Most evidence comes from high-income countries,[2,9,14-24,26-28] where more robust health systems may buffer harms. In contrast, household socioeconomic stressors and sociodemographic characteristics remain understudied in low-income settings where risks may be amplified.[17]

Understanding the long-term consequences of suicide exposure on mortality is essential for guiding public health and postvention efforts.[29,30] However, few population-based studies have examined these outcomes.[17,19] This study used nationwide administrative data from Brazil to investigate mortality outcomes among household members exposed to suicide in socioeconomically disadvantaged settings. Objectives were to (1) estimate the increased risk of all-cause and cause-specific mortality among household members exposed to suicide, (2) identify risk factors for subsequent suicide among these household members, and (3) assess timing of mortality after exposure. It was hypothesized that exposure to suicide increases mortality, with risks varying by timing, sociodemographic factors, and household conditions.

Methods

Ethical Considerations

Ethical approval was obtained from the Federal University of Bahia and Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Bahia. As no personally identifiable information was included, informed consent was waived. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Design and Data Sources

This nationwide longitudinal study used data from the 100 Million Brazilian Cohort (100MCohort) linked with the Brazilian Mortality Information System (SIM) (2001-2018).[31] The 100MCohort, established by the Centre for Data and Knowledge Integration for Health (CIDACS),[32] involves linkage between the Unified Registry for Social Programs (CadÚnico) and Brazilian Health Information Systems.[33] CadÚnico eligibility requires per capita monthly family income equal to half of the minimum wage or less.[34] From 2011 to 2018, CadÚnico included 131 697 800 individuals, with higher proportions of young people, female individuals, and urban residents. SIM is a nationwide health information system for recording mortality data, encompassing all deaths in the country and their causes.[35]

Data Linkage

Linking the 100MCohort baseline and SIM datasets (2001-2018) used a 2-step process based on 5 individual identifiers (name, date of birth, sex, mother's name, and municipality) via the CIDACS record linkage tool.[36] Exact matching was followed by similarity-score linkage for unmatched entries.

Accuracy was assessed through manual validation of a random subset and receiver operating characteristic analysis, with sensitivity and specificity exceeding 92% (eFigure 1 and eTable 1 in Supplement 1).

Study Population

This study included individuals aged 10 years or older at registration or who reached this age during follow-up (January 1, 2001, to December 31, 2018). Excluded individuals were (1) those aged above 110 years at registration and (2) individuals who registered in CadÚnico on the last day of the follow-up (December 31, 2018), died, or became exposed on the day of cohort enrollment (eFigure 2 in Supplement 1).

Exposure and Follow-up

Suicide survivors were defined as household members of the decedent, given their exposure to a suicide and likelihood of being personally affected by it.[19,29] In the 100MCohort, household members share a family and/or household code, and each individual has a unique identifier linked to socioeconomic and demographic characteristics. Using these codes, we identified all members of each household and the first suicide within it, referred to as the suicide index case. The exposed individuals were those who had a suicide index case in their household, identified by sharing the same household code. Unexposed individuals were classified as: (1) those who never had a suicide index case during the follow-up period or (2) those who had an suicide index case but were considered unexposed until the occurrence of that event.

Unexposed individuals were followed up from the time of their registration in the cohort baseline until 1 of the following occurrences: (1) death due to any cause (including suicide), (2) end of the follow-up (December 31, 2018), or (3) the date of the occurrence of the suicide index case within the same household. Exposed individuals were followed up from the occurrence of the suicide index case until 1 of the following: (1) death due to any cause (including suicide) or (2) end of the follow-up (December 31, 2018) (eFigure 3 in Supplement 1).

Primary and Secondary Outcomes

The primary outcome was all-cause mortality, defined as death from any cause as classified by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)*.[35] As suicide is an expected outcome in families with a history of suicide, the main analyses focused on all-cause mortality excluding suicide (*ICD-10* codes X60-X84) to avoid confounding. Separate analyses were conducted for all-cause mortality including suicide and for suicide-specific mortality to enable comparison and interpretation. Secondary outcomes included (1) other mortality due to external causes (*ICD-10* codes V00-Y99, excluding suicide); (2) the 5 most frequent specific causes of external mortality in our dataset: violence (X85-Y09), transport injuries (V01-V99), falls (W00-W19), accidental drowning (W65-W74), and accidental poisoning (X43); (3) mortality due to natural causes (all other causes excluding external causes); and (4) the most frequent specific natural causes of death, including diseases of the circulatory system (I00-I99), neoplasms (C00-D48), metabolic diseases (E70-E89), diseases of the respiratory system (J00-J99), and parasitic diseases (B65-B83).

Statistical Analysis

For the first objective, sex-specific age-standardized rates were estimated using person-year as the denominator and using the Brazilian 2015 official population projection as the standard.[33] A multivariable, time-varying Cox regression model was used to assess whether exposure to a household suicide was associated with subsequent mortality among surviving members. This approach considers changing variables and time-dependent covariates,[37] allowing exposure to be treated dynamically; individuals contributed person-time as unexposed until a household suicide occurred, after which they were classified as exposed (eFigure 3 in Supplement 1). Crude and

adjusted hazard ratios (HRs) were estimated with 95% CIs. Models were adjusted for confounders identified in prior literature, including sex, age, race, region, location of residence, urbanicity, unemployment, housing materials, water supply, sanitation, and waste. Race was derived from the CadÚnico database and self-reported as Asian, Black, Indigenous, Parda, or White. Parda (Portuguese for brown) denotes individuals of predominantly Black or mixed ancestry, including European, African, and Indigenous origins. The attributable risk percentage (%AR) was calculated using the Levin formula: %AR_exp = [(Incidence_exp − 1) ÷ (Incidence_exp − 1) + 1] × 100, to quantify the proportion of deaths attributable to exposure (exp).[38]

For the second objective, the focus was on individuals in households with a prior suicide. A multivariable Cox regression was used to examine factors associated with subsequent suicide or all-cause mortality. The final model, optimized through stepwise selection, included variables for (1) the sex and age of the index case and (2) the sex and age of surviving household members (measured at the time of the index case), as well as household conditions and geographic region. Household conditions were captured using a composite score from 0 to 4, where 0 indicates no access and 4 indicates full access to essential services (water supply, sanitation, adequate housing materials, and waste disposal). Two interaction terms (sex and age of the index case) were tested to evaluate whether the outcomes associated with other risk factors varied according to these characteristics. Details of model specification and covariates are provided in eAppendices 1, 2, 3, and 4 in Supplement 1.

Finally, the proportional mortality of subsequent deaths and suicide events by year of occurrence after the index case were calculated. Nearly half of these deaths occurred within the first 2 years, which guided the definition of the immediate period as 2 or fewer years and the distant period as 3 or more years. The analysis further assessed whether risk factors varied between immediate (≤2 years) and distant (≥3 years) follow-up periods by including multiplicative interaction terms between each covariate and a dichotomous variable indicating follow-up time. The model can be represented as follows: log[hazard(t)] = β_0 + β_1 (≥3 years period) + β_2 (*characteristic X*) + β_3 (≥3 years period × *characteristic X*), where *characteristic X* refers to an explanatory variable of interest, such as the sex of the index individual, age at death, or sex of surviving household members, among others. The interaction term (β_3) allows us to assess whether the association of characteristic X with the risk of the outcome (all-cause mortality or suicide) differs between the period shortly after the death (≤2 years) and the later period (≥3 years). Although the model includes a single variable, multiple factors were included simultaneously, each with its respective main association and interaction term with time since death, allowing us to evaluate time-varying associations. The joint significance of the interaction terms was tested using the Wald test.

HRs and 95% CIs were reported separately for each time interval. All analyses were performed using Stata version 15.1 (StataCorp LLC). A 2-sided $P < .05$ was considered statistically significant.

To address potential bias from differences in follow-up time between exposed and unexposed groups, we performed sensitivity analyses using (1) a doubly robust approach adjusting the main analysis by adding exposure time as a covariate, (2) restricting follow-up to cohort entry for exposed and unexposed, and (3) simulating equal follow-up durations. For analyses of immediate and distant periods, we also tested alternative cutoffs and time scales (≤1 year vs ≥2 years; ≤3 years vs ≥4 years). Data were analyzed from March 2023 to September 2025.

Results

The cohort consisted of 101 346 669 individuals from 26 594 713 households, with 167 475 individuals in the exposed group. There were 47 982 suicide index cases (eFigure 2 in Supplement 1). Compared with the nonexposed group, individuals exposed to suicide were more likely to be female (90 405 individuals [54%]), young people (aged 10-24 years: 111 791 individuals [67%]), Parda (82 407 individuals [53%]), and unemployed (162 916 individuals [97%]) (**Table 1**). The exposed group also included 11 070 (7%) Black and 57 726 (37%) White individuals.

Table 1. Description of Study Population by Exposure to an Index Suicide Case in the Same Household (N = 101 346 669)

Characteristic	Participants, No. (%)		*P* value[a]
	Nonexposure (n = 101 179 194)	Exposure (n = 167 475)	
Sex			
Male	47 658 742 (47)	77 070 (46)	<.001
Female	53 520 452 (53)	90 405 (54)	
Age cohort			
10-24 y	58 804 961 (58)	111 791 (67)	<.001
25-59 y	37 278 090 (37)	50 809 (30)	
60-110 y	5 096 143 (5.0)	4875 (2.9)	
Race[b]			
Asian descendants	372 702 (0.4)	506 (0.3)	<.001
Black	7 036 884 (7.5)	11 070 (7.1)	
Indigenous	538 453 (0.6)	3627 (2.3)	
Parda[c]	55 370 996 (59)	82 407 (53)	
White	31 068 881 (33)	57 726 (37)	
Unknown	6 791 278	12 139	
Region			
Northeast	40 065 572 (40)	61 754 (37)	<.001
North	10 465 502 (10)	16 459 (9.8)	
Southeast	32 322 337 (32)	45 742 (27)	
South	11 522 233 (11)	31 126 (19)	
Central-West	6 710 100 (6.6)	12 216 (7.3)	
Unknown	93 450	178	
Location residence			
Urban	73 144 808 (74)	113 151 (69)	<.001
Rural	25 327 550 (26)	51 598 (31)	
Unknown	2 706 836	2726	
Unemployed			
Yes	96 309 167 (95)	162 916 (97)	<.001
No	4 870 027 (4.8)	4559 (2.7)	
Construction materials			
Uninformed	3 630 860 (3.6)	3644 (2.2)	<.001
Bricks or cement	72 657 604 (72)	109 128 (65)	
Wood, vegetal materials, and other	24 890 730 (25)	54 703 (33)	
Sanitation			
Uninformed	4 301 559 (4.3)	4391 (2.6)	<.001
Public network	42 391 809 (42)	59 256 (35)	
Septic tank	14 932 195 (15)	27 551 (16)	
Homemade septic tank	24 675 659 (24)	45 457 (27)	
Ditch or other	14 877 972 (15)	30 820 (18)	
Water supply			
Uninformed	3 630 469 (3.6)	3634 (2.2)	<.001
Public network (running water)	68 163 602 (67)	107 549 (64)	
Well, natural sources, or other	29 385 123 (29)	56 292 (34)	
Waste			
Uninformed	3 630 901 (3.6)	3642 (2.2)	<.001
Public collection system	71 129 518 (70)	108 884 (65)	
Burned, buried, outdoor disposal, or other	26 418 775 (26)	54 949 (33)	

[a] Pearson χ^2 test.

[b] Race was self-reported.

[c] Parda, which translates from Portuguese as brown, is used to denote individuals whose racial background is predominantly Black and those with multiracial ancestry, including European, African, and Indigenous origins.

Risk of All-Cause and Specific-Cause Mortality

Exposure to a suicide index case was associated with a 32% higher risk of mortality when including suicide (HR, 1.32; 95% CI, 1.28-1.36), and 27% higher risk when excluding suicide (HR, 1.27; 95% CI, 1.23-1.31), compared with nonexposed individuals (**Figure 1**). Suicide-specific mortality risk was over 4 times higher among exposed household members (HR, 4.42; 95% CI, 3.86-5.07). Exposed members also had a higher risk of death from external causes (excluding suicide) (HR, 1.35; 95% CI, 1.27-1.44) and natural causes (HR, 1.23; 95% CI, 1.18-1.27). Among external causes, higher risks were observed for deaths due to falls (HR, 1.80; 95% CI, 1.31-2.44), drowning (HR, 1.49; 95% CI, 1.09-2.03), assault (HR, 1.38; 95% CI, 1.27-1.51), and transport crashes (HR, 1.26; 95% CI, 1.12-1.43). For natural causes, higher risks were found for circulatory diseases (HR, 1.20; 95% CI, 1.12-1.29), neoplasms (HR, 1.22; 95% CI, 1.11-1.33), metabolic conditions (HR, 1.27; 95% CI, 1.11-1.46), and respiratory diseases (HR, 1.27; 95% CI, 1.08-1.48), with no clear association for infectious diseases (HR, 1.09; 95% CI, 0.92-1.29) (Figure 1).

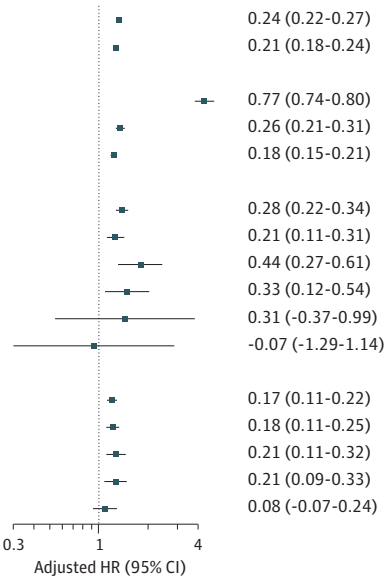
Main Risk Factors Among Surviving Household Members

Exposure to a female index case was associated with higher all-cause mortality excluding suicide among surviving household members (HR, 1.27; 95% CI, 1.16-1.40) compared with a male index case, but not with higher suicide (HR, 1.39; 95% CI, 0.94-2.06). Exposure to a younger index case (aged 10-24 years) was associated with higher all-cause mortality (HR, 1.16; 95% CI, 1.08-1.26) and suicide (HR, 1.68; 95% CI, 1.22-2.31) compared with an older index case (aged 60 years or older). An interaction showed that a young female index case was associated with lower risk of all-cause mortality (HR, 0.72; 95% CI, 0.61-0.84) relative to older male cases (**Table 2**).

Among surviving household members, male individuals had a 75% higher risk of all-cause mortality excluding suicide (HR, 1.75; 95% CI, 1.64-1.86) and over 3 times higher risk of suicide (HR, 3.58; 95% CI, 2.65-4.84) compared with female individuals. Compared with young survivors, risk of all-cause mortality was higher among those aged 25 to 59 years (HR, 3.81; 95% CI, 3.51-4.15) and those aged 60 years or older (HR, 24.13; 95% CI, 22.09-26.37), whereas suicide risk was higher

Figure 1. Cox Multivariate Model of the Association Between Suicide Index Case and the Risk of Mortality

Cause of death	Age-standardized rate, per person-years (95% CI)		Adjusted HR (95% CI)	PAF (95% CI)
	Unexposed	Exposed		
All-cause mortality				
With suicide	541.92 (541.92-541.93)	646.68 (646.67-646.68)	1.32 (1.28-1.36)	0.24 (0.22-0.27)
Without suicide	537.60 (537.60-537.61)	625.22 (625.22-625.23)	1.27 (1.23-1.31)	0.21 (0.18-0.24)
Cause-specific mortality				
Suicide	4.32 (4.31-4.32)	21.45 (21.45-21.46)	4.42 (3.86-5.07)	0.77 (0.74-0.80)
External cause (without suicide)	57.32 (57.31-57.32)	87.65 (87.65-87.66)	1.35 (1.27-1.44)	0.26 (0.21-0.31)
Nonexternal cause	480.29 (480.29-480.30)	537.56 (537.56-537.57)	1.23 (1.18-1.27)	0.18 (0.15-0.21)
External cause-specific mortality				
Assault	26.12 (26.12-26.13)	43.69 (43.69-43.70)	1.38 (1.27-1.51)	0.28 (0.22-0.34)
Transport related	17.68 (17.68-17.69)	23.38 (23.38-23.39)	1.26 (1.12-1.43)	0.21 (0.11-0.31)
Falls	4.74 (4.73-4.74)	7.01 (7.01-7.02)	1.80 (1.31-2.44)	0.44 (0.27-0.61)
Accidental drowning	2.17 (2.17-2.18)	3.60 (3.60-3.61)	1.49 (1.09-2.03)	0.33 (0.12-0.54)
Exposure smoke	0.34 (0.34-0.35)	0.45 (0.45-0.46)	1.45 (0.54-3.86)	0.31 (-0.37-0.99)
Accidental poisoning	0.23 (0.23-0.24)	0.22 (0.22-0.23)	0.93 (0.30-2.89)	-0.07 (-1.29-1.14)
Nonexternal cause-specific mortality				
Diseases in the circulatory system	165.83 (165.83-165.84)	184.03 (184.03-184.04)	1.20 (1.12-1.29)	0.17 (0.11-0.22)
Neoplasms	89.92 (89.92-89.93)	100.41 (100.41-100.42)	1.22 (1.11-1.33)	0.18 (0.11-0.25)
Metabolic diseases	37.52 (37.52-37.53)	45.30 (45.30-45.31)	1.27 (1.11-1.46)	0.21 (0.11-0.32)
Diseases in the respiratory system	27.55 (27.55-27.56)	30.86 (30.86-30.87)	1.27 (1.08-1.48)	0.21 (0.09-0.33)
Infectious disease	22.83 (22.83-22.83)	23.64 (23.64-23.64)	1.09 (0.92-1.29)	0.08 (-0.07-0.24)



Model adjusted for sex, age cohort, race, region, location residence, unemployed, construction materials, water supply, and waste. HR indicates hazard ratio; PAF, population attributable fraction.

among those aged 25 to 59 years (HR, 1.64; 95% CI, 1.25-2.14) but not among those aged 60 years or older (HR, 1.04; 95% CI, 0.52-2.06).

Better household conditions, reflected by having all 4 essential services, had lower risk of all-cause mortality (HR, 0.76; 95% CI, 0.69-0.85) and suicide (HR, 0.49; 95% CI, 0.33-0.73) compared with households without these essential services. Regionally, suicide risk was higher in the South (HR, 2.13; 95% CI, 1.51-3.01) and Central-West (HR, 2.89; 95% CI, 1.89-4.41) compared with the Northeast. For all-cause mortality excluding suicide, the South showed increased risk (HR, 1.17; 95% CI, 1.07-1.28) (Table 2).

Table 2. Cox Regression Model by Characteristics of the Index Suicide Case, Sociodemographic Characteristics of the Members, and Household Conditions Among Individuals Who Have Experienced a Previous Suicide Within the Same Household, 2001 to 2018

	All-cause mortality outcome (without suicide)		Suicide outcome	
Characteristic	HR (95% CI)	Adjusted HR (95% CI)	HR (95% CI)	Adjusted HR (95% CI)
Characteristics of the index case				
Sex of the index case				
Male	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Female	1.13 (1.05-1.22)	1.27 (1.16-1.40)	1.48 (1.12-1.96)	1.39 (0.94-2.06)
Age at death of the index case				
≥60 y	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
10-24 y	1.19 (1.11-1.27)	1.16 (1.08-1.26)	1.70 (1.30-2.21)	1.68 (1.22-2.31)
25-59 y	1.73 (1.55-1.94)	1.04 (0.92-1.19)	1.22 (0.69-2.16)	1.09 (0.54-2.17)
Sex of the index case and age at death of the index case				
Male ≥60 y	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Female 10-24 y	0.64 (0.55-0.75)	0.72 (0.61-0.84)	0.57 (0.32-1.03)	0.70 (0.39-1.27)
Female 25-59 y	1.47 (1.12-1.96)	0.94 (0.72-1.24)	1.78 (0.52-6.16)	1.88 (0.54-6.51)
Sociodemographic characteristics of surviving members				
Sex of surviving household members				
Female	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Male	1.50 (1.41-1.60)	1.75 (1.64-1.86)	3.54 (2.63-4.77)	3.58 (2.65-4.84)
Mortality age of the surviving household members at the date of occurrence of the Index case				
10-24 y	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
25-59 y	3.57 (3.29-3.89)	3.81 (3.51-4.15)	1.42 (1.09-1.85)	1.64 (1.25-2.14)
≥60 y	22.74 (20.84-24.82)	24.13 (22.09-26.37)	0.92 (0.47-1.82)	1.04 (0.52-2.06)
Household characteristics				
Living conditions[a]				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.02 (0.94-1.11)	1.03 (0.94-1.12)	0.43 (0.29-0.65)	0.47 (0.31-0.71)
2	0.96 (0.87-1.05)	0.99 (0.90-1.10)	0.62 (0.43-0.91)	0.61 (0.42-0.89)
3	0.78 (0.70-0.86)	0.79 (0.71-0.88)	0.34 (0.23-0.51)	0.33 (0.22-0.50)
4	0.73 (0.66-0.81)	0.76 (0.69-0.85)	0.43 (0.30-0.62)	0.49 (0.33-0.73)
Region				
Northeast	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
North	0.85 (0.75-0.97)	1.09 (0.96-1.23)	1.51 (0.94-2.43)	1.22 (0.75-1.98)
Southeast	1.04 (0.96-1.12)	1.09 (1.00-1.18)	1.00 (0.68-1.47)	1.15 (0.76-1.73)
South	1.09 (1.01-1.19)	1.17 (1.07-1.28)	2.05 (1.45-2.88)	2.13 (1.51-3.01)
Central-West	0.97 (0.85-1.10)	1.09 (0.95-1.24)	2.80 (1.84-4.25)	2.89 (1.89-4.41)

Abbreviation: HR, hazard ratio.

[a] Living conditions defined as household conditions measured using a composite score from 0 to 4, where 0 indicates no access and 4 indicates full access to essential services, including water supply, sanitation, adequate housing materials, and waste disposal.

Timing of Subsequent Deaths After the Index Case: Comparison of Immediate (≤2 Years) and Distant Events (>3 Years)

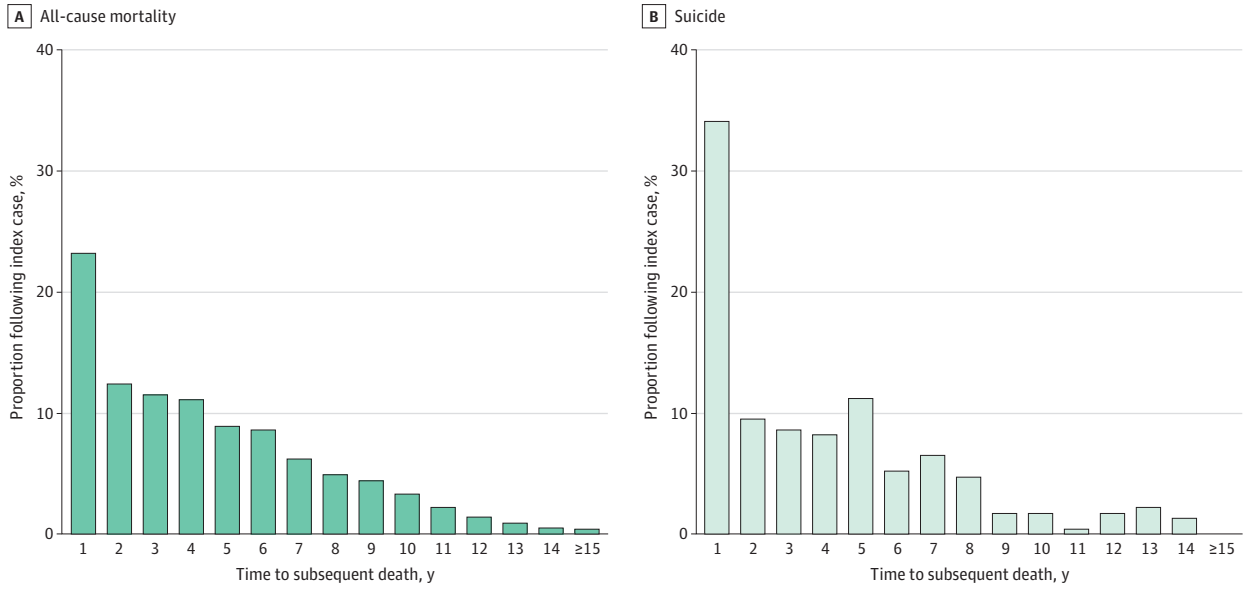
Most subsequent deaths, both all-cause and by suicide, occurred within 2 years of the index suicide. Among all-cause mortality (excluding suicide; 4009 individuals), 1429 (35.6%) occurred within 2 years (931 [23.2%] in year 1; 498 [12.4%] in year 2) (**Figure 2**). Among suicides (232 individuals), 101 (43.6%) occurred in the same period (79 [34.1%] in year 1; 22 [9.5%] in year 2). For all-cause mortality, no differences were observed between immediate (≤2 years) and distant (≥3 years) periods. For suicide, a time-dependent association was found; during the first 2 years, having a female index case was associated with higher suicide risk among survivors (HR, 1.72; 95% CI, 1.03-2.84; *P* = .03), an outcome not observed after 3 years (HR, 0.86; 95% CI, 0.58-1.28) (**Figure 3**). All sensitivity analyses yielded results consistent with those of the main model (eTables 6-9, eFigure 5 in Supplement 1). A summary of key findings and associated risk factors is provided in eFigure 6 in Supplement 1.

Discussion

This large-scale cohort study is the first we know of to examine timing and risk factors for all- and cause-specific mortality after household exposure to suicide. Exposure was associated with a 27% increased in all-cause mortality (excluding suicide) and over 4-fold higher suicide risk, with a population attributable fraction of 77%. Risks were elevated when the index case was younger or female, and when surviving household members were male, aged 25 to 59 years, or living in households with poor infrastructure. Over half of subsequent suicides occurred within the first 2 years, reinforcing the urgency of targeted early interventions (eFigure 7 in Supplement 1).

Prior research shows elevated suicide risk among individuals with a family history of suicide,[2,14-25] yet broader mortality outcomes remain underexplored.[9,26-28] In Taiwan, higher rates of suicide (rate ratio [RR], 4.61; 95% CI, 4.02-5.29) and accidental deaths (RR, 1.62; 95% CI, 1.43-1.84) were reported among first-degree relatives of suicide decedents.[27] Another study found increased risks of suicide (HRs up to 15.67; 95% CI, 2.09-117.41), homicide (HRs up to 23.26; 95% CI, 3.10-174.56), and dementia (HR, 4.41; 95% CI, 1.14-17.05) in suicide-exposed individuals, but not for

Figure 2. Proportion of Subsequent All-Cause Mortality (Excluding Suicide) and Suicide in Years

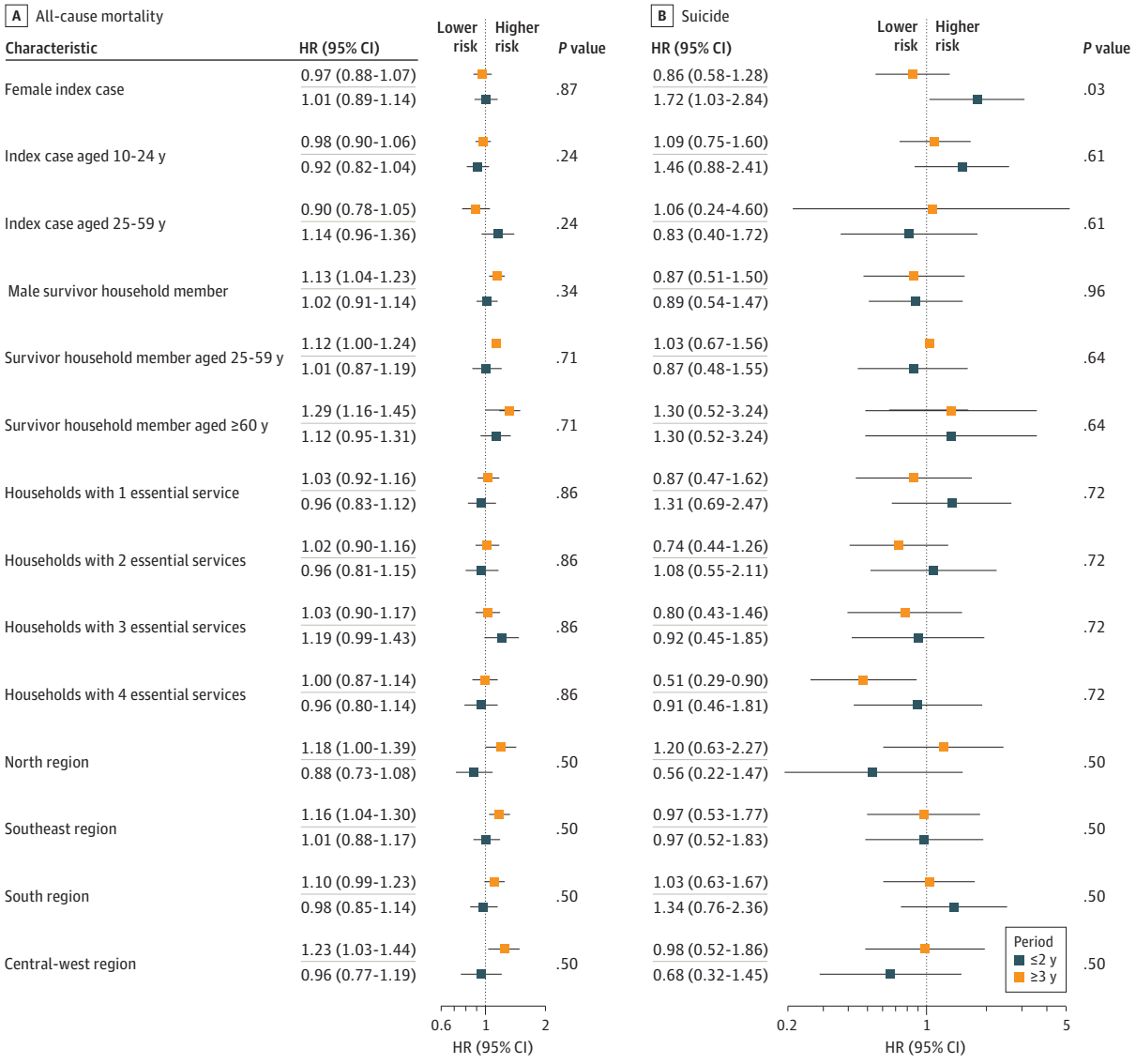


All-cause mortality (4009 individuals) and suicide (232 individuals).

all-cause mortality relative to unnatural deaths (HR, 0.95; 95% CI, 0.87-1.04).[28] The current study expands on existing evidence, showing that household suicide exposure is linked to higher risks of both suicide and all-cause mortality, including from metabolic, respiratory, circulatory diseases, and neoplasms. All major external and natural causes of death were elevated except parasitic diseases, which are likely more tied to environmental and socioeconomic factors than psychosocial stressors. The 442% increased risk of suicide observed in this study exceeds estimates from high-income countries such as Denmark (RR, 2.58; 95% CI, 1.84-3.61)[21] and South Korea (RR, 2.75; 95% CI, 2.55-2.97),[16] suggesting greater impact in settings characterized by heightened social and structural vulnerability.

The mechanisms linking family suicide history and increased mortality likely involve multiple pathways.[9,26-28] Suicide exposure is traumatic and often results in grief, guilt, stigma, and family disruption.[5-7] These factors are associated with suicide behaviors,[2,14-25] and contribute to

Figure 3. Factors Associated with Immediate (≤2 Years) and Distant (≥3 Years) Time-to-Event Mortality



P value represents the test of interaction between the time since the index case's death (≤2 years vs ≥3 years) and the respective characteristic under evaluation.
HR indicates hazard ratio.

depression, anxiety, PTSD, and substance use,[3-11,18] thereby leading to early death. Chronic stress may disrupt the hypothalamic-pituitary-adrenal axis, suppress immune function, and increase the risk of cardiovascular and metabolic disorders,[39] explaining elevated deaths from circulatory, respiratory, and metabolic diseases. Social and economic stressors may also play a role.[2,18] Suicide loss can trigger financial hardship, social withdrawal, family conflict, and caregiving burdens.[5-7] Male survivors and adults aged 25 to 59 years were especially affected, suggesting that adult men may face distinct challenges in coping with household suicide. Death of a younger index case (aged 10-24 years) also resulted in higher mortality risk, reflecting the destabilizing impact of an unexpected death and the profound grief it provokes.[20,21,40]

Over a third of all-cause deaths (35.6%) and nearly half of suicides (43.6%) occurred within 2 years of the index suicide. In the immediate aftermath of the suicide, family members often experience intense grief marked by guilt, blame, and stigma,[2,5-7,18] leading to enduring physical, psychological, and psychosomatic difficulties.[18] These challenges highlight the urgent need for family-centered interventions after suicide loss.[12] Although the bereaved may express a notable desire to participate in suicide support groups,[2,18] access to mental health services or specialized care for survivors remains scarce, especially in lower-resource contexts such as Brazil.[41] In the current study, survivors living in better housing conditions showed lower mortality risk, reinforcing the role of socioeconomic factors in mitigating outcomes after suicide loss.[42,43]

Strengths and Limitations

Previous studies have been limited to high-income settings with small samples and lacked population-based comparison groups. This study leveraged a large population-based cohort to overcome these gaps. This design provides sufficient power to examine rare outcomes and exposures, including suicide occurrence and recurrence within households. Most earlier studies used case-control designs, which precluded estimation of population-level measures such as suicide, relative risks, and attributable risks. Other studies focused only on individuals with recorded deaths, limiting comparisons by family suicide history. The current approach enabled the estimation of these rates and risks and the assessment of the interval between an index suicide and subsequent suicide within the same household, offering important insights for prevention strategies.

Some limitations are unmeasured confounders that could introduce bias and the lack of information regarding parental status, as well as access to mental health care. It is noteworthy that some causes of death, such as ill-defined or unknown causes, events of undetermined intent, and accidental deaths, may conceal hidden suicides, potentially influencing the findings. Moreover, this study population was composed of low-income individuals, limiting generalizability. Additionally, suicide may be underregistered; however, in Brazil, external causes of death undergo systematic review by medical-legal institutes, and the SIM database is recognized for its high quality, minimizing misclassification.[44]

Conclusions

This cohort study of 101 346 669 individuals in Brazil found that household exposure to suicide resulted in over 4-fold increase in subsequent suicide risk and a 27% rise in all-cause mortality (excluding suicide) among surviving members (eFigure 7 in the Supplement). These far-reaching health consequences, associated with external and nonexternal causes, were most pronounced in the first 2 years, highlighting the urgency for early intervention. These findings call for integrated postvention strategies including bereavement care, psychosocial support, and clinical follow-up, especially in lower-resource settings, to advance global mental health equity and support Sustainable Development Goal 3.4: "reducing premature mortality from noncommunicable diseases and promoting mental well-being."[45]

ARTICLE INFORMATION

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REFERENCES

1. World Health Organization. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. Accessed April 2, 2024. https://www.who.int/publications-detail-redirect/9789241565707

2. Spillane A, Larkin C, Corcoran P, Matvienko-Sikar K, Riordan F, Arensman E. Physical and psychosomatic health outcomes in people bereaved by suicide compared to people bereaved by other modes of death: a systematic review. *BMC Public Health*. 2017;17(1):939. doi:10.1186/s12889-017-4930-3

3. Brent D, Melhem N, Donohoe MB, Walker M. The incidence and course of depression in bereaved youth 21 months after the loss of a parent to suicide, accident, or sudden natural death. *Am J Psychiatry*. 2009;166(7):786-794. doi:10.1176/appi.ajp.2009.08081244

4. Levi-Belz Y, Gilo T. Emotional distress among suicide survivors: the moderating role of self-forgiveness. *Front Psychiatry*. 2020;11:341. doi:10.3389/fpsyt.2020.00341

5. Tal Young I, Iglewicz A, Glorioso D, et al. Suicide bereavement and complicated grief. *Dialogues Clin Neurosci*. 2012;14(2):177-186. doi:10.31887/DCNS.2012.14.2/iyoung

6. Mitchell AM, Kim Y, Prigerson HG, Mortimer MK. Complicated grief and suicidal ideation in adult survivors of suicide. *Suicide Life Threat Behav*. 2005;35(5):498-506. doi:10.1521/suli.2005.35.5.498

7. Mitchell AM, Kim Y, Prigerson HG, Mortimer-Stephens M. Complicated grief in survivors of suicide. *Crisis*. 2004;25(1):12-18. doi:10.1027/0227-5910.25.1.12

8. Mitchell AM, Terhorst L. PTSD symptoms in survivors bereaved by the suicide of a significant other. *J Am Psychiatr Nurses Assoc*. 2017;23(1):61-65. doi:10.1177/1078390316673716

9. Erlangsen A, Runeson B, Bolton JM, et al. Association between spousal suicide and mental, physical, and social health outcomes: a longitudinal and nationwide register-based study. *JAMA Psychiatry*. 2017;74(5):456-464. doi:10.1001/jamapsychiatry.2017.0226

10. Bolton JM, Au W, Leslie WD, et al. Parents bereaved by offspring suicide: a population-based longitudinal case-control study. *JAMA Psychiatry*. 2013;70(2):158-167. doi:10.1001/jamapsychiatry.2013.275

11. Ljung T, Sandin S, Långström N, Runeson B, Lichtenstein P, Larsson H. Offspring death and subsequent psychiatric morbidity in bereaved parents: addressing mechanisms in a total population cohort. *Psychol Med*. 2014;44(9):1879-1887. doi:10.1017/S0033291713002572

12. World Health Organization. Preventing suicide: a global imperative. Accessed April 2, 2024. https://www.who.int/publications-detail-redirect/9789241564779

13. Lichtenthal WG, Roberts KE, Donovan LA, et al. Investing in bereavement care as a public health priority. *Lancet Public Health*. 2024;9(4):e270-e274. doi:10.1016/S2468-2667(24)00030-6

14. Kõlves K, Milner A, Värnik P. Suicide rates and socioeconomic factors in Eastern European countries after the collapse of the Soviet Union: trends between 1990 and 2008. *Sociol Health Illn*. 2013;35(6):956-970. doi:10.1111/1467-9566.12011

15. Kõlves K, Zhao Q, Ross V, Hawgood J, Spence SH, de Leo D. Suicide and sudden death bereavement in Australia: a longitudinal study of family members over 2 years after death. *Aust N Z J Psychiatry*. 2020;54(1):89-98. doi:10.1177/0004867419882490

16. Jang J, Park SY, Kim YY, et al. Risks of suicide among family members of suicide victims: a nationwide sample of South Korea. *Front Psychiatry*. 2022;13:995834. doi:10.3389/fpsyt.2022.995834

17. Calderaro M, Baethge C, Bermpohl F, Gutwinski S, Schouler-Ocak M, Henssler J. Offspring's risk for suicidal behaviour in relation to parental death by suicide: systematic review and meta-analysis and a model for familial transmission of suicide. *Br J Psychiatry*. 2022;220(3):121-129. doi:10.1192/bjp.2021.158

18. Spillane A, Matvienko-Sikar K, Larkin C, Corcoran P, Arensman E. What are the physical and psychological health effects of suicide bereavement on family members? An observational and interview mixed-methods study in Ireland. *BMJ Open*. 2018;8(1):e019472. doi:10.1136/bmjopen-2017-019472

19. Andriessen K, Rahman B, Draper B, Dudley M, Mitchell PB. Prevalence of exposure to suicide: a meta-analysis of population-based studies. *J Psychiatr Res*. 2017;88:113-120. doi:10.1016/j.jpsychires.2017.01.017

20. Qin P, Mortensen PB. The impact of parental status on the risk of completed suicide. *Arch Gen Psychiatry*. 2003;60(8):797-802. doi:10.1001/archpsyc.60.8.797

21. Qin P, Agerbo E, Mortensen PB. Suicide risk in relation to family history of completed suicide and psychiatric disorders: a nested case-control study based on longitudinal registers. *Lancet*. 2002;360(9340):1126-1130. doi:10.1016/S0140-6736(02)11197-4

22. Runeson B, Asberg M. Family history of suicide among suicide victims. *Am J Psychiatry*. 2003;160(8):1525-1526. doi:10.1176/appi.ajp.160.8.1525

23. Agerbo E. Risk of suicide and spouse's psychiatric illness or suicide: nested case-control study. *BMJ*. 2003;327(7422):1025-1026. doi:10.1136/bmj.327.7422.1025

24. Agerbo E. Midlife suicide risk, partner's psychiatric illness, spouse and child bereavement by suicide or other modes of death: a gender specific study. *J Epidemiol Community Health*. 2005;59(5):407-412. doi:10.1136/jech.2004.024950

25. Tidemalm D, Runeson B, Waern M, et al. Familial clustering of suicide risk: a total population study of 11.4 million individuals. *Psychol Med*. 2011;41(12):2527-2534. doi:10.1017/S0033291711000833

26. Rostila M, Saarela J, Kawachi I. The forgotten griever: a nationwide follow-up study of mortality subsequent to the death of a sibling. *Am J Epidemiol*. 2012;176(4):338-346. doi:10.1093/aje/kws163

27. Chen YY, Gunnell D, Wu CK, Hu YH, Lee PC. All-cause and cause-specific mortality in parents after the death of a child in Taiwan: a population-based cohort study. *Psychosom Med*. 2023;85(3):221-230. doi:10.1097/PSY.0000000000001182

28. Ho HY, Chen YL. Causes of death in individuals exposed to spousal, parental, and child suicide: a nationwide population-based cohort comparison study. *Eur J Epidemiol*. 2023;38(11):1165-1174. doi:10.1007/s10654-023-01055-8

29. Jordan JR. Lessons learned: forty years of clinical work with suicide loss survivors. *Front Psychol*. 2020;11:766. doi:10.3389/fpsyg.2020.00766

30. Jordan JR. Postvention is prevention—the case for suicide postvention. *Death Stud*. 2017;41(10):614-621. doi:10.1080/07481187.2017.1335544

31. Barreto ML, Ichihara MY, Pescarini JM, et al. Cohort profile: the 100 Million Brazilian Cohort. *Int J Epidemiol*. 2022;51(2):e27-e38. doi:10.1093/ije/dyab213

32. Barreto ML, Ichihara MY, Almeida BA, et al. The Centre for Data and Knowledge Integration for Health (CIDACS): linking health and social data in Brazil. *Int J Popul Data Sci*. 2019;4(2):1140.

33. Informações de Saúde (TABNET). DATASUS. Accessed April 3, 2024. https://datasus.saude.gov.br/informacoes-de-saude-tabnet/

34. VIS DATA 3 beta. Accessed April 3, 2024. https://aplicacoes.cidadania.gov.br/vis/data3/v.php?q[]=r6JtZI%2B0gbBtxKW25rV%2FfmdhhJFkl21kmK19Zm11ZmqmaX7KmZO2OqfOnJm%2B6lianbSon7Stv8OcaJLHlNawmJi2wKmpa5Rwr2%2BGf2uMvNSnO6qUOeTDlZuulqfipbavqozH0JXcoqa83bOTn62jrehrfX9naL3Cn92ibtHtwpl3g5ub5ayyiXKgzM5W5V5bnd2zk628mZnfmrp9d4yNl2mjbme84MCopbWWruKvrq2djsTKn9OeprzrvJauraiZ25%2BssZybytBlmm5jl7W7qamtp6PcYnd%2FZ1143m7Qnp%2FQ4lianbSon7ROs6%2BjoLycbt2yoNnMwpWqvJ6e2p2ybpuSd6eU1wDgyeSup1yqmqjen7axoI67wqaKrZjJ6m12q7Som5l%2Frrv62sPKlI2CptHkupWwsaubmZ2ybn2OxCTg1qaU0Judo566mq2ZZm2RnJvK0FOzf3qim39kbXhYit6rsLOloczCn4qhmH3evJahuqmv65ptspigd6eU1wDgyeSup1yqmqjen7axoPD4O5zLsFPB6m2Efo6xqrQ%3D

35. World Health Organization. *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*. World Health Organization; 1992.

36. Barbosa GCG, Ali MS, Araujo B, et al. CIDACS-RL: a novel indexing search and scoring-based record linkage system for huge datasets with high accuracy and scalability. *BMC Med Inform Decis Mak*. 2020;20(1):289. doi:10.1186/s12911-020-01285-w

37. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6(7):121. doi:10.21037/atm.2018.02.12

38. Mansournia MA, Altman DG. Population attributable fraction. *BMJ*. 2018;360:k757. doi:10.1136/bmj.k757

39. Sic A, Cvetkovic K, Manchanda E, Knezevic NN. Neurobiological implications of chronic stress and metabolic dysregulation in inflammatory bowel diseases. *Diseases*. 2024;12(9):220. doi:10.3390/diseases12090220

40. Rostila M, Saarela J, Kawachi I. Suicide following the death of a sibling: a nationwide follow-up study from Sweden. *BMJ Open*. 2013;3(4):e002618. doi:10.1136/bmjopen-2013-002618

41. Oliveira Alves FJ, Fialho E, Paiva de Araújo JA, et al. The rising trends of self-harm in Brazil: an ecological analysis of notifications, hospitalisations, and mortality between 2011 and 2022. *Lancet Reg Health Am*. 2024;31:100691. doi:10.1016/j.lana.2024.100691

42. Machado DB, Williamson E, Pescarini JM, et al. Relationship between the Bolsa Família national cash transfer programme and suicide incidence in Brazil: a quasi-experimental study. *PLoS Med*. 2022;19(5):e1004000. doi:10.1371/journal.pmed.1004000

43. Alves FJO, Machado DB, Barreto ML. Effect of the Brazilian cash transfer programme on suicide rates: a longitudinal analysis of the Brazilian municipalities. *Soc Psychiatry Psychiatr Epidemiol*. 2019;54(5):599-606. doi:10.1007/s00127-018-1627-6

44. Rebouças P, Alves FJ, Ferreira A, et al. Avaliação da qualidade do Sistema Brasileiro de Informações sobre Mortalidade (SIM): uma scoping review. *Cien Saude Colet*. 2025;30(1):e08462023. doi:10.1590/1413-81232025301.08462023

45. United Nations Department of Economic and Social Affairs. Goal 3: Ensure healthy lives and promote well-being for all at all ages. Accessed October 31, 2025. https://sdgs.un.org/goals/goal3

SUPPLEMENT 1.

eAppendix 1. Data Sources and Linkage of the Datasets

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Patients with metastatic non–small-cell lung cancer have a substantial symptom burden and may receive aggressive care at the end of life. We examined the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease.

METHODS

We randomly assigned patients with newly diagnosed metastatic non–small-cell lung cancer to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone. Quality of life and mood were assessed at baseline and at 12 weeks with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale and the Hospital Anxiety and Depression Scale, respectively. The primary outcome was the change in the quality of life at 12 weeks. Data on end-of-life care were collected from electronic medical records.

RESULTS

Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better quality of life than did patients assigned to standard care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better quality of life], 98.0 vs. 91.5; P=0.03). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, P=0.01). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, P=0.05), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, P=0.02).

CONCLUSIONS

Among patients with metastatic non–small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival. (Funded by an American Society of Clinical Oncology Career Development Award and philanthropic gifts; ClinicalTrials.gov number, NCT01038271.)

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N Engl J Med 2010;363:733-42.

The quality of care and the use of medical services for seriously ill patients are key elements in the ongoing debate over reform of the U.S. health care system.[1] Oncologic care is central to this debate, largely because anticancer treatments are often intensive and costly.[2] Comprehensive oncologic services for patients with metastatic disease would ideally improve the patients' quality of life and facilitate the efficient allocation of medical resources. Palliative care, with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services.[3,4] However, palliative care has traditionally been delivered late in the course of disease to patients who are hospitalized in specialized inpatient units or as a consultative service for patients with uncontrolled symptoms.[5,6] Previous studies have suggested that late referrals to palliative care are inadequate to alter the quality and delivery of care provided to patients with cancer.[7,8] To have a meaningful effect on patients' quality of life and end-of-life care, palliative care services must be provided earlier in the course of the disease.

Metastatic non–small-cell lung cancer, the leading cause of death from cancer worldwide,[9] is a debilitating disease that results in a high burden of symptoms and poor quality of life; the estimated prognosis after the diagnosis has been established is less than 1 year.[10-12] We previously found that introducing palliative care shortly after diagnosis was feasible and acceptable among outpatients with metastatic non–small-cell lung cancer.[13] The goal of the current study was to examine the effect of early palliative care integrated with standard oncologic care on patient-reported outcomes, the use of health services, and the quality of end-of-life care among patients with metastatic non–small-cell lung cancer. We hypothesized that patients who received early palliative care in the ambulatory care setting, as compared with patients who received standard oncologic care, would have a better quality of life, lower rates of depressive symptoms, and less aggressive end-of-life care.

Methods

Study Design

From June 7, 2006, to July 15, 2009, we enrolled ambulatory patients with newly diagnosed metastatic non–small-cell lung cancer in a nonblinded, randomized, controlled trial of early palliative care integrated with standard oncologic care, as compared with standard oncologic care alone. The study was performed at Massachusetts General Hospital in Boston. Eligible patients were enrolled within 8 weeks after diagnosis and were randomly assigned to one of the two groups in a 1:1 ratio without stratification. Patients who were assigned to early palliative care met with a member of the palliative care team, which consisted of board-certified palliative care physicians and advanced-practice nurses, within 3 weeks after enrollment and at least monthly thereafter in the outpatient setting until death. Additional visits with the palliative care service were scheduled at the discretion of the patient, oncologist, or palliative care provider.

General guidelines for the palliative care visits in the ambulatory setting were adapted from the National Consensus Project for Quality Palliative Care and were included in the study protocol.[14] Using a template in the electronic medical record, palliative care clinicians documented the care they provided according to these guidelines (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Specific attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of the patient.[14,15] Patients who were randomly assigned to standard care were not scheduled to meet with the palliative care service unless a meeting was requested by the patient, the family, or the oncologist; those who were referred to the service did not cross over to the palliative care group or follow the specified palliative care protocol. All the participants continued to receive routine oncologic care throughout the study period. Before enrollment in the study was initiated, the protocol was approved by the Dana Farber/Partners CancerCare institutional review board. All participants provided written informed consent. The protocol, including the statistical analysis plan, is available at NEJM.org. All the authors attest that the study was performed in accordance with the protocol and the statistical analysis plan.

Patients

Patients who presented to the outpatient thoracic oncology clinic were invited by their medical on-

cologists to enroll in the study; all the medical oncologists in the clinic agreed to approach, recruit, and obtain consent from their patients. Physicians were encouraged, but not required, to offer participation to all eligible patients; no additional screening or recruitment measures were used. Patients were eligible to participate if they had pathologically confirmed metastatic non–small-cell lung cancer diagnosed within the previous 8 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (with 0 indicating that the patient is asymptomatic, 1 that the patient is symptomatic but fully ambulatory, and 2 that the patient is symptomatic and in bed <50% of the day)[16] and were able to read and respond to questions in English. Patients who were already receiving care from the palliative care service were not eligible for participation in the study.

PATIENT-REPORTED MEASURES

Health-related quality of life was measured with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, which assesses multiple dimensions of the quality of life (physical, functional, emotional, and social well-being) during the previous week.[17] In addition, the lung-cancer subscale (LCS) of the FACT-L scale evaluates seven symptoms specific to lung cancer. The primary outcome of the study was the change from baseline to 12 weeks in the score on the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale.

Mood was assessed with the use of both the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire 9 (PHQ-9).[18,19] The 14-item HADS, which consists of two subscales, screens for symptoms of anxiety and depression in the previous week. Subscale scores range from 0, indicating no distress, to 21, indicating maximum distress; a score higher than 7 on either HADS subscale is considered to be clinically significant. The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). A major depressive syndrome was diagnosed if a patient reported at least five of the nine symptoms of depression on the PHQ-9, with one of the five symptoms being either anhedonia or depressed mood. Symptoms had to be present for more than half the time, except for the symptom of suicidal thoughts, which was included in the diagnosis if it was present at any time.

MEASURES OF HEALTH CARE USE

Data were collected from the electronic medical record on the use of health services and end-of-life care, including anticancer therapy, medication prescriptions, referral to hospice, hospital admissions, emergency department visits, and the date and location of death. Patients were classified as having received aggressive care if they met any of the following three criteria: chemotherapy within 14 days before death, no hospice care, or admission to hospice 3 days or less before death.[20-22] Finally, we assessed whether patients' resuscitation preferences were documented in the outpatient electronic medical record.[23]

DATA COLLECTION

Participants completed baseline questionnaires before randomization. Follow-up assessments of quality of life and mood were performed at 12 weeks (or at an outpatient clinic visit within 3 weeks before or after that time point). Participants who had no scheduled clinic visits within this period received the questionnaires by mail. When responses on questionnaires were incomplete, research staff documented the reasons for which the participant did not give a full response.

STATISTICAL ANALYSIS

Data obtained through December 1, 2009, were included in the analyses. The primary outcome was the change in the score on the TOI from baseline to 12 weeks. We estimated that with 120 patients, the study would have 80% power to detect a significant between-group difference in the change in the TOI score from baseline to 12 weeks, with a medium effect size of 0.5 SD.[24] The protocol was amended in August 2008 to allow for the enrollment of an additional 30 participants in order to compensate for the loss of any patients to follow-up.

Statistical analyses were performed with the use of SPSS software, version 16.0 (SPSS). Descriptive statistics were used to estimate the frequencies, means, and standard deviations of the study variables. Differences between study groups in baseline characteristics and clinical outcomes were assessed with the use of two-sided Fisher's exact tests and chi-square tests for categorical

variables and independent-samples Student's t-tests for continuous variables. Multivariate linear regression analyses, adjusted for baseline scores, were used to examine the effect of early palliative care on quality-of-life outcomes. For intention-to-treat analyses, we used the conservative method of carrying baseline values forward to account for all missing patient-reported outcome data, including data that were missing owing to death. Survival time was calculated from the date of enrollment to the date of death with the use of the Kaplan–Meier method. Data from patients who were alive at the last follow-up (December 1, 2009) were censored on that date. A Cox proportional-hazards model was used to assess the effect of early palliative care on survival, with adjustment for demographic characteristics and baseline ECOG performance status.

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

A total of 151 patients were enrolled in the study (see the figure in the Supplementary Appendix). The percentage of patients enrolled was similar for each of the thoracic oncologists in the clinic.

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Standard Care (N=74)	Early Palliative Care (N=77)	P Value†
Age — yr	64.87±9.41	64.98±9.73	0.94
Female sex — no. (%)	36 (49)	42 (55)	0.52
Race — no. (%)‡			0.06§
White	70 (95)	77 (100)	
Black	3 (4)	0	
Asian	1 (1)	0	
Hispanic or Latino ethnic group‡	1 (1)	1 (1)	1.00
Marital status — no. (%)			1.00
Married	45 (61)	48 (62)	
Single	9 (12)	9 (12)	
Divorced or separated	12 (16)	12 (16)	
Widowed	8 (11)	8 (10)	
ECOG performance status — no. (%)¶			0.24
0	30 (41)	26 (34)	
1	35 (47)	46 (60)	
2	9 (12)	5 (6)	
Presence of brain metastases — no. (%)	19 (26)	24 (31)	0.48
Initial anticancer therapy — no. (%)			0.87‖
Platinum-based combination chemotherapy	35 (47)	35 (45)	
Single agent	3 (4)	9 (12)	
Oral EGFR tyrosine kinase inhibitor	6 (8)	6 (8)	
Radiotherapy	26 (35)	27 (35)	
Chemoradiotherapy	3 (4)	0	
No chemotherapy	1 (1)	0	
Receipt of initial chemotherapy as part of a clinical trial — no. (%)	20 (27)	16 (21)	0.45
Never smoked or smoked ≤10 packs/yr — no./total no. (%)	16/73 (22)	18/76 (24)	0.85
Assessment of mood symptoms — no./total no. (%)			
HADS**			
Anxiety subscale	24/72 (33)	28/77 (36)	0.73
Depression subscale	18/72 (25)	17/77 (22)	0.70
PHQ-9 major depressive syndrome††	12/72 (17)	9/76 (12)	0.48

Table 1. (Continued.)

Variable	Standard Care (N=74)	Early Palliative Care (N=77)	P Value†
Scores on quality-of-life measures‡‡			
FACT-L scale	91.7±16.7	93.6±16.5	0.50
Lung-cancer subscale	18.7±4.4	20.1±4.4	
Trial Outcome Index	55.3±13.1	56.2±13.4	

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group, EFGR epidermal growth factor receptor, FACT-L Functional Assessment of Cancer Therapy–Lung, HADS Hospital Anxiety and Depression Scale, and PHQ-9 Patient Health Questionnaire 9.
† P values were calculated with the use of two-sided chi-square and Fisher's exact tests for categorical variables and the independent-samples Student's t-tests for continuous variables.
‡ Race or ethnic group was self-reported.
§ The P value is for the between-group comparison of the proportions of patients who were white and those who were members of a minority group (black and Asian), calculated with the use of Fisher's exact test.
¶ An ECOG performance status of 0 indicates that the patient is asymptomatic, 1 that the patient is symptomatic but fully ambulatory, and 2 that the patient is symptomatic and in bed less than 50% of the day.
‖ The P value is for the between-group comparison of the proportion of patients receiving platinum-based combination chemotherapy and the proportion receiving other treatments, calculated with the use of Fisher's exact test.
** The HADS consists of two subscales, one for symptoms of anxiety and one for symptoms of depression. Subscale scores range from 0, indicating no distress, to 21, indicating maximum distress; a score higher than 7 indicates clinically meaningful anxiety or depression.
†† The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). A major depressive syndrome was diagnosed if a patient reported at least five of the nine symptoms of depression on the PHQ-9, with one of the five symptoms being either anhedonia or depressed mood. Symptoms had to be present for more than half the time, except for the symptom of suicidal thoughts, which was included in the diagnosis if it was present at any time.
‡‡ The quality of life was assessed with the use of three measures: the FACT-L scale, on which scores range from 0 to 136, with higher scores indicating a better quality of life; the lung-cancer subscale of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index, which is the sum of the scores on the lung-cancer, physical well-being, and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating a better quality of life).

No significant differences in demographic characteristics or overall survival were seen between the study participants and eligible patients who were not enrolled in the study. The baseline characteristics were well matched between the two study groups (Table 1). Known prognostic factors, including age, sex, ECOG performance status, presence or absence of brain metastases, smoking status, and initial anticancer therapy, were also balanced between the study groups. Although genetic testing was not routinely performed, the proportions of patients with mutations in the epidermal growth factor gene (*EGFR*) were similar between the study groups among the patients who underwent testing (9% in the palliative care group and 12% in the standard-treatment group, P=0.76). No significant between-group differences were seen in baseline quality of life or mood symptoms.

PALLIATIVE-CARE VISITS

All the patients assigned to early palliative care, except for one patient who died within 2 weeks after enrollment, had at least one visit with the palliative care service by the 12th week. The average number of visits in the palliative care group was 4 (range, 0 to 8). Ten patients who received standard care (14%) had a palliative care consultation in the first 12 weeks of the study, primarily to address the management of symptoms, with seven patients having one visit and three having two visits.

QUALITY-OF-LIFE AND MOOD OUTCOMES

A comparison of measures of quality of life at 12 weeks showed that the patients assigned to early palliative care had significantly higher scores than did those assigned to standard care, for the total FACT-L scale, the LCS, and the TOI, with effect sizes in the medium range (Table 2). Patients in the palliative care group had a 2.3-point increase in mean TOI score from baseline to 12 weeks, as compared with a 2.3-point decrease in the standard care group (P=0.04) (Fig. 1). With the use of linear regression to control for baseline quality-of-life values, the group assignment significantly predicted scores at 12 weeks on the total FACT-L scale (adjusted difference in mean

Table 2. Bivariate Analyses of Quality-of-Life Outcomes at 12 Weeks.*

Variable	Standard Care (N=47)	Early Palliative Care (N=60)	Difference between Early Care and Standard Care (95% CI)	P Value†	Effect Size‡
FACT-L score	91.5±15.8	98.0±15.1	6.5 (0.5–12.4)	0.03	0.42
LCS score	19.3±4.2	21.0±3.9	1.7 (0.1–3.2)	0.04	0.41
TOI score	53.0±11.5	59.0±11.6	6.0 (1.5–10.4)	0.009	0.52

* Plus–minus values are means ±SD. Quality of life was assessed with the use of three scales: the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, on which scores range from 0 to 136, with higher scores indicating better quality of life; the lung-cancer subscale (LCS) of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating better quality of life).

† The P value was calculated with the use of two-sided Student's t-tests for independent samples.

‡ The effect size was determined with the use of Cohen's d statistic, which is a measure of the difference between two means (in this case, the mean in the group assigned to early palliative care group minus the mean in the group assigned to standard care) divided by a standard deviation for the pooled data. According to the conventional classification, an effect size of 0.20 is small, 0.50 moderate, and 0.80 large.

[±SE] scores, 5.4±2.4; 95% confidence interval [CI], 0.7 to 10.0; P=0.03) and the TOI (adjusted difference in mean scores, 5.2±1.8; 95% CI, 1.6 to 8.9; P=0.005), but not on the LCS (adjusted difference in mean scores, 1.0±0.6; 95% CI, −0.2 to 2.3; P=0.12). In addition, the percentage of patients with depression at 12 weeks, as measured by the HADS and PHQ-9, was significantly lower in the palliative care group than in the standard care group, although the proportions of patients receiving new prescriptions for antidepressant drugs were similar in the two groups (approximately 18% in both groups, P=1.00) (Fig. 2). The percentage of patients with elevated scores for symptoms of anxiety did not differ significantly between the groups.

The figure in the Supplementary Appendix includes an explanation of missing data according to study group. There was no significant association between missing data on patient-reported outcomes at 12 weeks and any baseline characteristic (although there was a trend toward a significant association between missing data and assigned treatment [P=0.07]). When we carried the baseline scores of the participants forward for the missing data on patient-reported outcomes, all primary treatment effects were replicated with respect to quality of life (P=0.04 for the 12-week FACT-L score, P=0.01 for the 12-week LCS score, P=0.04 for the 12-week TOI score, and P=0.04 for the mean change from baseline to 12 weeks in the TOI score) and mood (P=0.04 for the comparison of patients with elevated scores on the HADS depression subscale, and P=0.02 for the comparison of patients with symptoms of major depression on the PHQ-9).

END-OF-LIFE CARE

At the time of the analysis of end-of-life care, 105 participants (70%) had died; the median duration of follow-up among participants who died was 5.7 months. Within this subsample, a greater percentage of patients in the group assigned to standard care than in the group assigned to early palliative care received aggressive end-of-life care (54% [30 of 56 patients] vs. 33% [16 of 49 patients], P=0.05). In addition, fewer patients in the standard care group than in the palliative care group had resuscitation preferences documented in the outpatient electronic medical record (28% [11 of 39 patients who had preferences documented during the course of the study] vs. 53% [18 of 34 patients], P=0.05). The study did not have adequate power to examine specific indicators of aggressive care at the end of life. However, analyses of various measures of utilization, such as rates of hospitalization and emergency department visits (Table 2 in the Supplementary Appendix), as well as the duration of hospice care (median duration, 11 days in the palliative care group vs. 4 days in the standard care group; P=0.09 with the use of the Wilcoxon rank-sum test), suggested an improvement in the quality of care with early palliative care. Despite receiving less aggressive end-of-life care, patients in the palliative care group had significantly longer survival than those in the standard care group (median survival, 11.6 vs. 8.9 months; P=0.02) (Fig. 3).

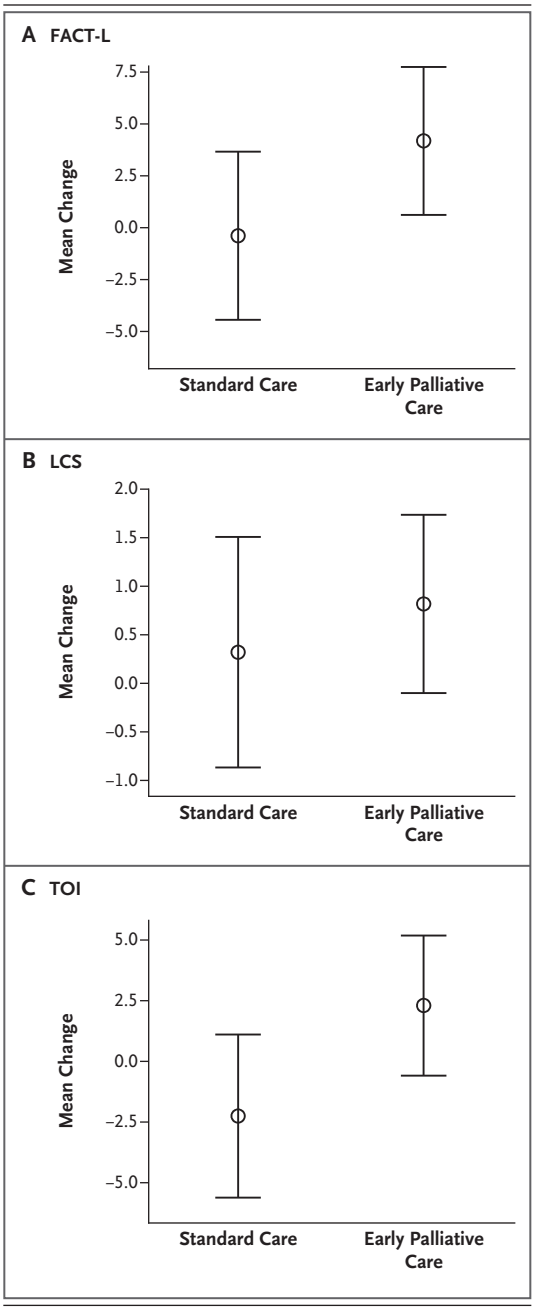

Figure 1. Mean Change in Quality-of-Life Scores from Baseline to 12 Weeks in the Two Study Groups.

Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, on which scores range from 0 to 136, with higher scores indicating a better quality of life; the lung-cancer subscale (LCS) of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating a better quality of life). With study group as the independent variable, two-sided independent-samples Student's t-tests showed a trend toward a significant between-group difference in the mean (±SD) change in scores from baseline to week 12 on the FACT-L scale (−0.4±13.8 in the standard care group vs. 4.2±13.8 in the palliative care group; difference between groups, 4.6; 95% confidence interval [CI], −0.8 to 9.9; P=0.09) (Panel A), no significant between-group difference in the mean change in scores on the LCS (0.3±4.0 and 0.8±3.6 in the two groups, respectively; difference between groups, 0.5; 95% CI, −1.0 to 2.0; P=0.50) (Panel B), and a significant between-group difference in the mean change in scores on the TOI (−2.3±11.4 vs. 2.3±11.2; difference between groups, 4.6; 95% CI, 0.2 to 8.9; P=0.04) (Panel C). Data are from the 47 patients in the standard care group and the 60 patients in the palliative care group who completed the 12-week assessments. I bars indicate 95% confidence intervals.

DISCUSSION

This study shows the effect of palliative care when it is provided throughout the continuum of care for advanced lung cancer. Early integration of palliative care with standard oncologic care in patients with metastatic non–small-cell lung cancer resulted in survival that was prolonged by approximately 2 months and clinically meaningful improvements in quality of life and mood. Moreover, this care model resulted in greater documentation of resuscitation preferences in the outpatient electronic medical record, as well as less aggressive care at the end of life. Less aggressive end-of-life care did not adversely affect survival. Rather, patients receiving early palliative care, as compared with those receiving standard care alone, had improved survival. Previous data have shown that a lower quality of life and depressed mood are associated with shorter survival among patients with metastatic non–small-cell lung cancer.[25-27] We hypothesize that improvements in both of these outcomes among patients assigned to early palliative care may account for the observed survival benefit. In addition, the integration of palliative care with standard oncologic care may facilitate the optimal and appropriate administration of anticancer therapy, especially during the final months of life. With earlier referral to a hospice program, patients may receive care that results in better management of symptoms, leading to stabilization of their condition and prolonged survival. These hypotheses require further study.

Improving quality of life and mood in patients

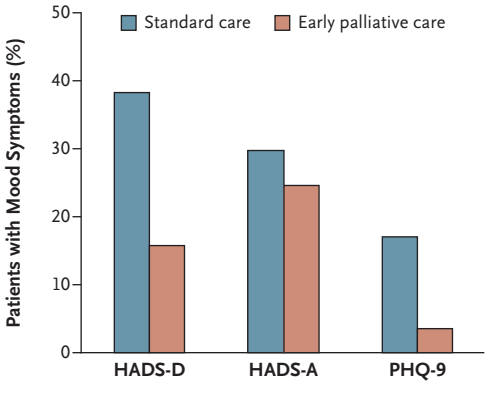

Figure 2. Twelve-Week Outcomes of Assessments of Mood.

Depressive symptoms were assessed with the use of the Hospital Anxiety and Depression Scale (HADS), which consists of two subscales, one for symptoms of anxiety (HADS-A) and one for symptoms of depression (HADS-D) (subscale scores range from 0, indicating no distress, to 21, indicating maximum distress; a score higher than 7 on either HADS subscale is considered to be clinically significant) and with the use of the Patient Health Questionnaire 9 (PHQ-9). The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). A major depressive syndrome was diagnosed if a patient reported at least five of the nine symptoms of depression on the PHQ-9, with one of the five symptoms being either anhedonia or depressed mood. Symptoms had to be present for more than half the time, except for the symptom of suicidal thoughts, which was included in the diagnosis if it was present at any time. The percentages of patients with mood symptoms, assessed on the basis of each of these measures, in the group assigned to standard treatment and the group assigned to early palliative care, respectively, are as follows: HADS-D, 38% (18 of 47 patients) versus 16% (9 of 57), P=0.01; HADS-A, 30% (14 of 47 patients) and 25% (14 of 57), respectively; P=0.66; and PHQ-9, 17% (8 of 47 patients) versus 4% (2 of 57); P=0.04. The analyses were performed with the use of a two-sided Fisher's exact test.

with metastatic non–small-cell lung cancer is a formidable challenge, given the progressive nature of the illness.[28] The improvement we observed in the quality of life among patients assigned to early palliative care, as indicated by a mean change in the TOI score by 12 weeks that was approximately 5 points higher in the palliative care group than in the standard care group, is similar to the improvement in the quality of life that has been observed among patients who have a response to cisplatin-based chemotherapy.[29] Most studies show that there is a deterioration in the quality of life over time, which is consistent with the results in the standard care group in our study.[30-32] Despite similar cancer therapies in our two study groups, the patients assigned to early palliative care had an improved quality of life, as compared with those receiving standard care. Rates of depression also differed significantly between the groups, with approximately half as many patients in the palliative care group as in the standard care group reporting clinically significant depressive symptoms on the HADS, and this effect was not due to a between-group difference in the use of antidepressant agents.

To date, evidence supporting a benefit of palliative care is sparse, with most studies having notable methodologic weaknesses, especially with respect to quality-of-life outcomes.[8] One study with sufficient power to examine quality-of-life outcomes showed that among patients receiving radiation therapy, a multidisciplinary intervention focused on education, behavioral modification, and coping style resulted in improvements in the quality of life.[33] A recent study showed that Project ENABLE (Educate, Nurture, Advise, Before Life Ends), a telephone-based, psychoeducational program for patients with advanced cancer, significantly improved both quality of life and mood.[34] However, the percentage of patients who completed the study assessments was somewhat low, and the study did not use a traditional palliative care model.

Our study also showed that early outpatient palliative care for patients with advanced cancer can alter the use of health care services, including care at the end of life. Other studies of outpatient palliative care have failed either to investigate these outcomes or to show an effect on the use of resources.[5,34,35] In our trial, significantly more patients in the group assigned to early palliative care than in the standard care group had resuscitation preferences documented in the outpatient electronic medical record, an essential step in clarifying and ensuring respect for patients' wishes about their care at the end of life.[36] Early introduction of palliative care also led to less aggressive end-of-life care, including reduced chemotherapy and longer hospice care. Given the trends toward aggressive and costly care near the end of life among patients with cancer, timely introduction of palliative care may serve to mitigate unnecessary and burdensome personal and societal costs.[20,37]

Our study has several advantages over previous studies, in which investigators have often relied on referrals to palliative care instead of using a recruitment approach designed to obtain a representative sample.[5,35] Because all patients with a new diagnosis of metastatic non–small-cell lung cancer were eligible for enrollment in our study, we extended the generalizability of our findings. Another strength of our trial was the low rate of loss to follow-up and the high percentage of participants who completed the study assessments. In addition, the dropout rate by week 12 was less than 1%, further supporting the feasibility and acceptability of early palliative care. Finally, the trial was adequately powered to detect changes in both quality of life and mood, and we prospectively collected data on end-of-life care.

Several limitations of the study deserve mention. It was performed at a single, tertiary care site with a specialized group of thoracic oncology providers and palliative care clinicians, thereby limiting generalization of the results to other care settings or patients with other types of cancer. In addition, because the sample lacked diversity with respect to race and ethnic group, we were unable to assess the effect of these important factors on study outcomes. Although we used a randomized, controlled design, both the patients and the clinicians were aware of the study assignments. To account for possible influences of care that are not specific to the palliative care provided, follow-up investigations should include a control group that receives a similar amount of attention. In addition, we did not deny palliative care consultations to participants receiving standard care, and a small minority of patients in the standard care group was seen by the palliative care team. The data from these patients were analyzed with the data from their assigned study group (standard care), a factor that may have diluted our findings. Finally, carrying the last observation forward for all missing data in the intention-to-treat analyses is a conservative approach; therefore, the actual treatment effect of early palliative care may be greater than we report.

Early integration of palliative care for patients with metastatic non–small-cell lung cancer is a clinically meaningful and feasible care model that has effects on survival and quality of life that are similar to the effects of first-line chemotherapy in such patients.[28,38,39] As compared with the study participants who received standard care, those who were assigned to early palliative care had improved mood, more frequent documentation of resuscitation preferences, and less aggressive end-of-life care. Although our findings must be replicated in a variety of care settings and cancer populations, the results nonetheless offer great promise for alleviating distress in patients with metastatic disease and addressing critical concerns regarding the use of health care services at the end of life.

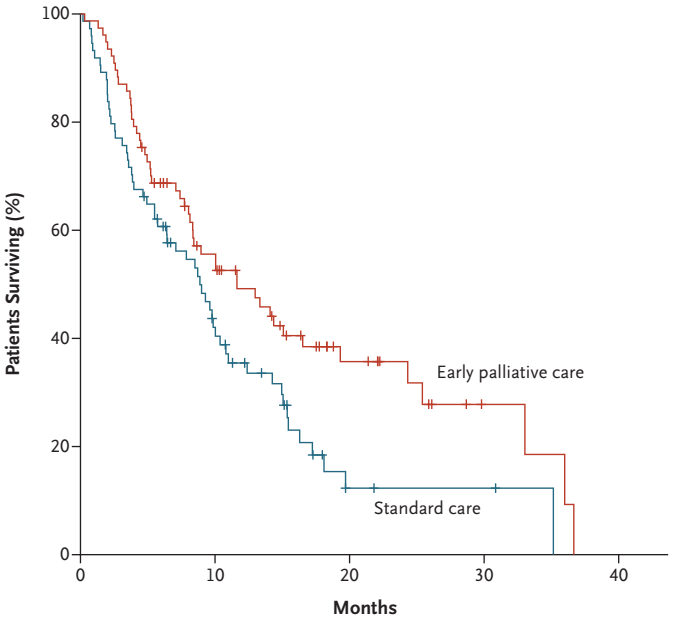

Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.
Survival was calculated from the time of enrollment to the time of death, if it occurred during the study period, or to the time of censoring of data on December 1, 2009. Median estimates of survival were as follows: 9.8 months (95% confidence interval [CI], 7.9 to 11.7) in the entire sample (151 patients), 11.6 months (95% CI, 6.4 to 16.9) in the group assigned to early palliative care (77 patients), and 8.9 months (95% CI, 6.3 to 11.4) in the standard care group (74 patients) (P=0.02 with the use of the log-rank test). After adjustment for age, sex, and baseline Eastern Cooperative Oncology Group performance status, the group assignment remained a significant predictor of survival (hazard ratio for death in the standard care group, 1.70; 95% CI, 1.14 to 2.54; P=0.01). Tick marks indicate censoring of data.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Mongan JJ, Ferris TG, Lee TH. Options for slowing the growth of health care costs. N Engl J Med 2008;358:1509-14.
2. Weinstein MC, Skinner JA. Comparative effectiveness and health care spending — implications for reform. N Engl J Med 2010;362:460-5.
3. Ferris FD, Bruera E, Cherny N, et al. Palliative cancer care a decade later: accomplishments, the need, next steps — from the American Society of Clinical Oncology. J Clin Oncol 2009;27:3052-8.
4. Levy MH, Back A, Benedetti C, et al. NCCN clinical practice guidelines in oncology: palliative care. J Natl Compr Canc Netw 2009;7:436-73.
5. Follwell M, Burman D, Le LW, et al. Phase II study of an outpatient palliative care intervention in patients with metastatic cancer. J Clin Oncol 2009;27:206-13.
6. Jordhøy MS, Fayers P, Loge JH, Ahlner-Elmqvist M, Kaasa S. Quality of life in palliative cancer care: results from a cluster randomized trial. J Clin Oncol 2001;19:3884-94.
7. Morita T, Akechi T, Ikenaga M, et al. Late referrals to specialized palliative care service in Japan. J Clin Oncol 2005;23:2637-44.
8. Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. JAMA 2008;299:1698-709.
9. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
10. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 2000;18:893-903.
11. Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. Br J Cancer 1995;71:633-6.
12. Lutz S, Norrell R, Bertucio C, et al. Symptom frequency and severity in patients with metastatic or locally recurrent lung cancer: a prospective study using the Lung Cancer Symptom Scale in a community hospital. J Palliat Med 2001;4:157-65.
13. Temel JS, Jackson VA, Billings JA, et al. Phase II study: integrated palliative care in newly diagnosed advanced non-small-cell lung cancer patients. J Clin Oncol 2007;25:2377-82.
14. Clinical practice guidelines for quality palliative care. 2nd ed. Pittsburgh: National Consensus Project, 2009. (Accessed July 23, 2010, at www.nationalconsensusproject.org.)
15. Jackson VA, Jacobsen JC, Greer J, et al. Components of early intervention outpatient palliative care consultation in patients with incurable NSCLC. J Clin Oncol 2009;27:Suppl:20635. abstract.
16. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
17. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12:199-220.
18. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361-70.
19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
20. Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? J Clin Oncol 2008;26:3860-6.
21. American Society of Clinical Oncology Quality Oncology Practice Initiative. ASCO QOPI summary of measures. Fall 2009. (Accessed July 23, 2010, at http://qopi.asco.org/Documents/QOPIFall2009MeasuresSummary8-18-09.pdf.)
22. Tang ST, Wu SC, Hung YN, Chen JS, Huang EW, Liu TW. Determinants of aggressive end-of-life care for Taiwanese cancer decedents, 2001 to 2006. J Clin Oncol 2009;27:4613-8.
23. Temel JS, Greer JA, Admane S, et al. Code status documentation in the outpatient electronic medical records of patients with metastatic cancer. J Gen Intern Med 2010;25:150-3.
24. Cella D. The Functional Assessment of Cancer Therapy–Lung and Lung Cancer Subscale assess quality of life and meaningful symptom improvement in lung cancer. Semin Oncol 2004;31:Suppl 9:11-5.
25. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the Multicenter Italian Lung Cancer in the Elderly Study. J Clin Oncol 2005;23:6865-72.
26. Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. J Clin Oncol 2009;27:5816-22.
27. Pirl WF, Temel JS, Billings A, et al. Depression after diagnosis of advanced non-small cell lung cancer and survival: a pilot study. Psychosomatics 2008;49:218-24.
28. Brown J, Thorpe H, Napp V, et al. Assessment of quality of life in the supportive care setting of the Big Lung Trial in non-small-cell lung cancer. J Clin Oncol 2005;23:7417-27.
29. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol 2002;55:285-95.
30. Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000;18:623-31.
31. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002;94:173-81.
32. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2000;18:122-30.
33. Rummans TA, Clark MM, Sloan JA, et al. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. J Clin Oncol 2006;24:635-42.
34. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 2009;302:741-9.
35. Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ. The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. Arch Intern Med 2004;164:83-91.
36. Walling A, Lorenz KA, Dy SM, et al. Evidence-based recommendations for information and care planning in cancer care. J Clin Oncol 2008;26:3896-902.
37. Emanuel EJ, Ash A, Yu W, et al. Managed care, hospice use, site of death, and medical expenditures in the last year of life. Arch Intern Med 2002;162:1722-8.
38. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311:899-909.
39. Spiro SG, Rudd RM, Souhami RL, et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax 2004;59:828-36.

Does Gut Microbiome Composition Influence the Efficacy of Psychiatric Drugs?

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Anxiety, biomarkers, depression, gut microbiome, microbiome composition.

SUMMARY

Altered gut microbiome profiles correlate with anxiety and depression in humans, and work in animal models has identified specific bacterial taxa and/or microbiome-derived metabolites that influence complex emotional behaviours. Intriguingly, many pharmaceuticals, including widely used oral treatments for anxiety and depression, can be chemically modified by microbes in the gastrointestinal tract, which may lead to drug inactivation. The authors highlight the importance of integrating research across microbial culture systems, animal models, and multi-omics analyses of clinical cohorts to gain mechanistic insights into whether microbiome composition determines efficacy, bioavailability, and tolerability of neuropsychiatric medications. This hypothesis, if validated, may have profound implications for personalised drug treatment plans and microbiome-based biomarker development.

THE RECIPROCAL RELATIONSHIP BETWEEN THE GUT MICROBIOME AND MEDICATIONS

The gut microbiome, comprising a staggering 3.8×10^{13} bacteria along with microscopic fungi, archaea, and viruses in humans,[1] plays crucial roles in shaping and maintaining host health. Gut microbes support a wide range of physiological functions including digestion, immune modulation, metabolism, and neuronal signaling. Disruptions in host-microbe interactions are associated with a range of human diseases, such as inflammatory bowel disease (IBD),[2] cancer,[3] Type 2 diabetes,[4] and neurological disorders.[5]

The gut microbiome is highly dynamic, with community composition influenced by intrinsic factors such as host genetics,[6] but also strongly determined by extrinsic/environmental contributors,[7] including diet and medication.[8] Because diet and drugs are modifiable, understanding the interactions between environmental factors and the gut microbiome offers an exciting and tractable opportunity for development of personalised medicines.

Most pharmaceuticals are administered orally. These substances are either absorbed in the small intestine, where the microbiome is sparse, or pass to the colon, where the densest and most diverse microbial communities reside. Additionally, drugs absorbed in the small intestine may be modified (or not) and secreted back into the intestine, creating new opportunities for exposure to the gut microbiome.[9] Consumption of antibiotics, unsurprisingly, has profound effects on the gut microbiome. Acute exposure to a single course of antibiotics can result in the transient reduction or loss of microbial taxa that are important for basic metabolic functions such as carbohydrate fermentation,[10] energy production, bile acid transformation,[11] and lipid absorption. While most individuals treated with antibiotics experience a rapid recovery of microbiome composition, for some it may take up to 6 months to fully recover their original (pre-drug) microbiome.[12] Loss of community stability and, consequently, compromise of normal metabolic functions of the microbiome may lead to opportunistic infections,[12,13] deficits in gut barrier integrity,[14]

weakening of the immune system,[15,16] and other unintended consequences. While antibiotics likely have the most profound impact on microbiome function, emerging evidence suggests that other medications may also compromise the microbiome, albeit to a subtler degree.

The vast majority of pharmaceutical drugs were developed against human targets (e.g., proteins, molecules, metabolic pathways), are diverse in structure, and are often consumed for extended periods of time, making it challenging to predict their direct or indirect effects on the microbiome. However, some drug–microbiome interactions have been uncovered. The common Type 2 diabetes medication metformin alters gut microbiome composition in patients, increasing microbial taxa that promote glucose metabolism and thereby increasing its therapeutic effect.[17] Methotrexate, a first-line treatment for rheumatoid arthritis, alters microbiome composition in patients and in human microbiome colonised mice, with transplantation of a drug-modified microbiome into drug-naïve mice being sufficient to reduce immune activation.[18] The benzisoxazole ring structure in risperidone, an atypical antipsychotic used for schizophrenia and bipolar disorder, is chemically modified by gut microbes, leading to its rapid excretion and thus potentially reducing efficacy and altering dosing regimens in ways that may vary between patients.[19]

Informed by these findings, there is growing interest in understanding how the gut microbiome may be influenced by, and may influence the efficacy of, various drug classes. Emerging evidence has identified novel microbial transformations of drugs that may alter the intended outcomes of medications.[9,20] Given the emerging and likely intricate relationship between gut bacteria and brain function, drug–microbiome interactions in the context of neuropsychiatric disorders represent a particularly interesting area of study. This perspective will first examine how the gut microbiome influences drug metabolism *in vivo*, drawing from studies in mice and humans with anxiety and major depressive disorder (MDD). The authors will then review known drug–microbiome interactions, primarily through examples beyond neuropsychiatric medications, as these well-characterised cases provide insights into the methodologies needed for future study of microbial metabolism of psychiatric drugs. Finally, the authors will discuss how integrating these approaches can provide an actionable framework for understanding the role of microbial influences on the efficacy and other features of psychiatric drugs.

THE GUT MICROBIOME AND BRAIN HEALTH: INSIGHTS FROM ANXIETY AND DEPRESSION

Anxiety disorders represent the most common class of neuropsychiatric conditions, and are characterised by a persistent avoidance response even in the absence of imminent danger.[21] Often co-occurring with depression,[22] which is marked by a prolonged loss of interest in activities, anxiety disorders significantly impact quality of life in up to a quarter of the USA and European populations.[23,24]

In recent years, studies conducted in both mouse models and human cohorts have described a functional role for the gut microbiome in the development of anxiety and depression (**Figure 1A**). The gut microbiome is stereotypically altered in individuals with anxiety or MDD,[25,26] and is speculated to affect symptoms via altered neurotransmitter production,[27] inflammation/cytokines,[28] the hypothalamic–pituitary–adrenal (HPA) axis,[29] vagus nerve,[27] and other potential mechanisms. These associations are supported by animal

models. Germ-free mice, which are raised without any exposure to microbes, exhibit reduced anxiety-like behaviour, and the reintroduction of a normal microbiome early in life is sufficient to restore anxiety-like traits of standard laboratory mice.[30] Transplantation of microbiomes from mice that have experienced chronic stress into naïve recipient mice induces behaviours consistent with depression, and supplementation with *Lactobacillus* alleviates this effect.[31]

The gut and brain communicate through various pathways (neuronal, endocrine, immunological) and these interactions involve factors that can be influenced by a diverse array of microbes and their products. For instance, treatment with the bacterium *Lactobacillus rhamnosus* (JB-1) has been shown to alleviate anxiety and depression-like behaviours in mice.[27] This effect occurs through the differential regulation of GABA receptors in the brain and is dependent on the vagus nerve, as vagotomised mice do not exhibit the same behavioural improvements when treated with *L. rhamnosus* (**Figure 1B**). Gut bacteria can also produce small molecule metabolites that then travel to the brain and alter cell function: the gut microbial metabolite 4-ethylphenyl sulfate (4-EPS) impairs oligodendrocyte differentiation in mice and increases anxiety-like behaviour.[32] In contrast, treating mice with the human commensal *Bacteroides fragilis* is able to alleviate anxiety-like and autism-associated features (**Figure 1C**).[33]

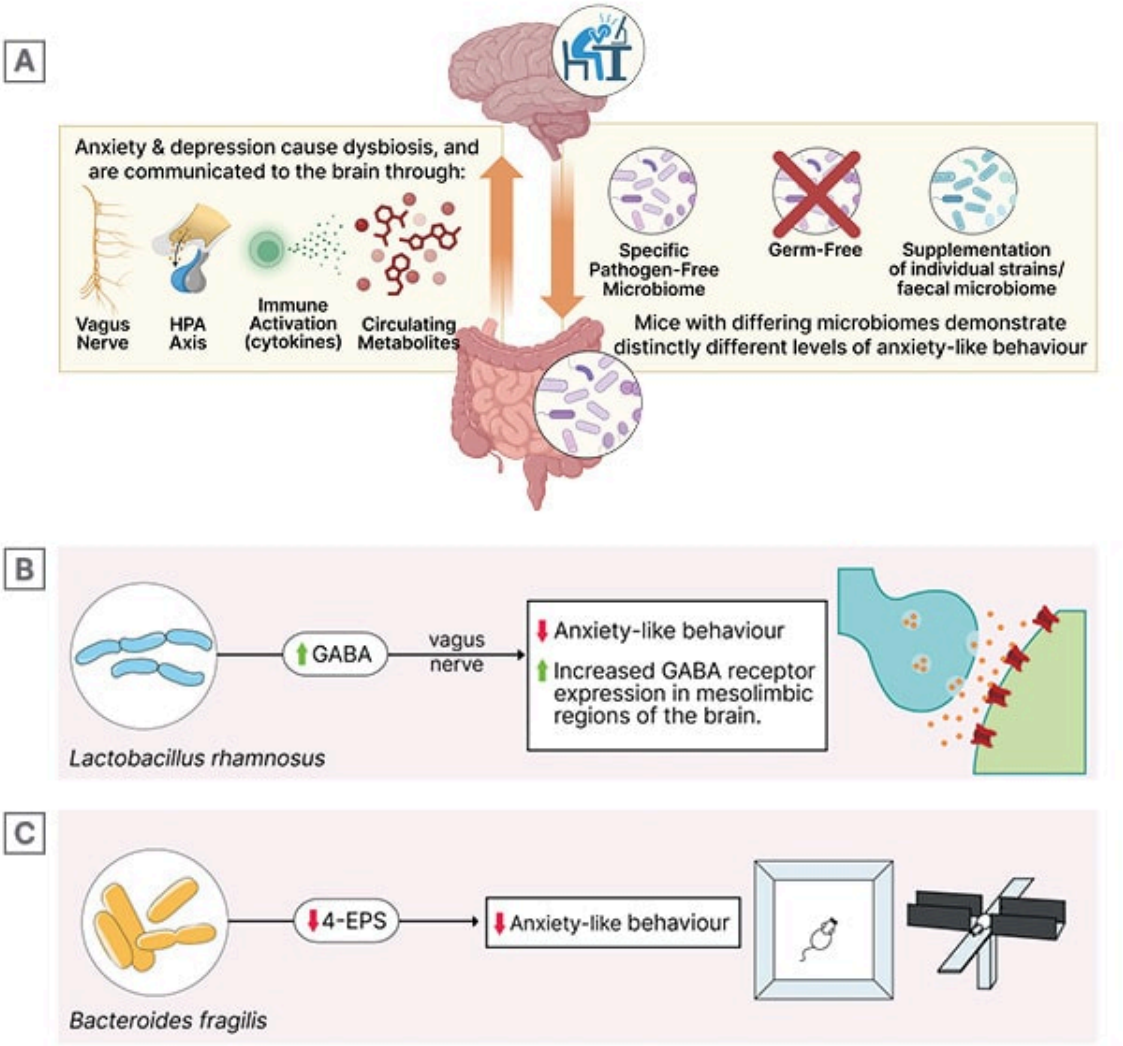

Figure 1: The microbiome and microbially-derived metabolites modulate host nervous system function.

Figure 1A is generated on Biorender.com.

In humans, large cohort studies surveying the microbiomes of depressed patients have revealed stereotypical alterations. Notably, MDD patients often show depletion of genera such as *Subdoligranulum* and *Coprococcus*, and an increase in *Eggerthella*, alongside changes in their metabolomes, particularly increased lipid metabolism.[26,34] A recent study integrated microbiome sequencing data from faecal samples of individuals with anxiety and depressive disorders, including those taking medications, to train machine learning algorithms that could successfully predict both the presence of these disorders and medication use based on microbiome profiles alone.[35] While effect sizes in human studies remain modest and may necessitate further replication, research to date on the potential pathogenic or protective effects of the gut microbiome in neuropsychiatric conditions represents an exciting frontier of research at the intersection of microbiology, neuroscience, and human health.

Microbiome Modulation of Neuropsychiatric Drugs

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are first-line treatments for both anxiety and MDD.[36] While these drug classes have been shown to be more effective than placebo for generalised anxiety disorder, their benefits are often accompanied by a therapeutic lag and significant variability in response rates, particularly in terms of long-term acceptability and sustained efficacy.[37] Given that SSRIs and SNRIs are orally administered, an important question is whether their interaction with the gut microbiome contributes to the substantial differences in therapeutic acceptability observed across patient populations. Interindividual variations in gut microbiome composition may influence drug metabolism and bioavailability, potentially explaining why some patients respond better to treatment than others.

Recent studies with high-throughput, *in vitro* culture-based screening systems have revealed extensive drug–microbiome interactions (**Figure 2**). In one study, researchers exposed 76 individual strains of diverse human gut bacterial taxa to over one hundred commonly prescribed drugs, including medications for anxiety.[38] This work found that metabolic reactions were taxon-specific; i.e., *Bacteroidetes* primarily hydrolysed drugs with ester or amide groups, while most other strains metabolised drugs containing a nitro or azide group. Of note, 10% of the strains chemically transformed anxiolytics, significantly reducing active drug levels in culture, with the SSRI fluoxetine emerging as the most widely metabolised anxiolytic across isolated bacterial strains. Another study incubated different complex communities derived from human faecal samples with drugs used to treat anxiety, again finding that microbiome composition can broadly influence drug metabolism.[39] Some communities had the metabolic capacity to degrade specific drugs, while others did not, highlighting interindividual variability in microbiome-driven drug metabolism.

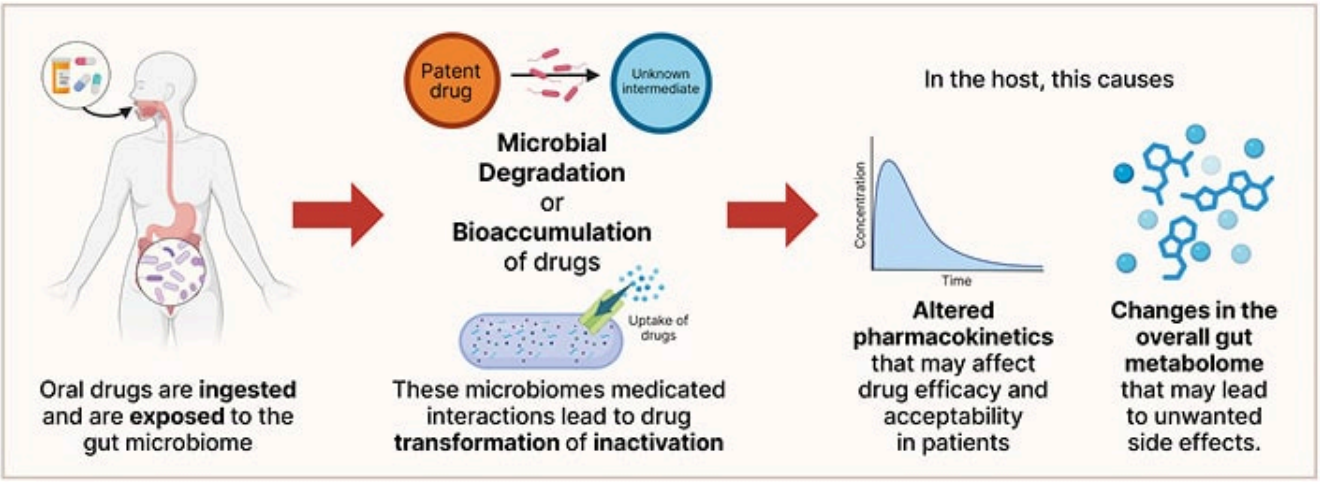

Figure 2: The microbiome modulates drugs, potentially affecting their therapeutic function in the host. Created on Biorender.com.

Researchers have also leveraged publicly available repositories to develop models to predict drug–microbiome interactions, such as SIMMER (Similarity algorithms that Identify MicrobioMe Enzymatic Reactions)[40] and AGORA2 (Assembly of Gut Organisms through Reconstruction and Analysis, version 2).[41] SIMMER combines metagenome-assembled genomes, protein homology, and enzyme databases to predict bacterial drug metabolism. This tool identified candidate gut bacterial enzymes, primarily carboxypeptidase G2-like enzymes, with sequence similarity to an environmental enzyme known to hydrolyse methotrexate.[40] Experimental testing of strains containing these enzymes confirmed methotrexate degradation. AGORA2 provides a resource for reconstructing metabolic pathways from metagenomic datasets, and incorporates clinical parameters such as BMI and age to facilitate rapid prediction of drug metabolism in epidemiological cohorts.[41] Both SIMMER and AGORA2 provide interactive frameworks, allowing researchers to prioritise microbial species, gene products, and pathways of particular relevance for a given disorder and drug class.

While high-throughput screening and large-scale dataset analyses have provided valuable insights, efforts to fully characterise drug–microbiome interactions remain ongoing, with only a few examples to date that have identified products of drug metabolism and even fewer cases tested functionally. For instance, Levodopa (L-DOPA), the first-line treatment for Parkinson's disease, is degraded by *Eggerthella lenta* and *Enterococcus faecalis*.[42] These bacterial species were shown to contain enzymes for conversion of L-DOPA into m-tyramine through decarboxylation and dihydroxylation, which may reduce L-DOPA bioavailability and impact treatment efficacy. Another well-known example of a drug–microbiome interaction is 5-aminosalicylic acid (5-ASA), used to treat IBD, whose efficacy is reduced by microbial metabolism.[43] By longitudinally monitoring IBD patients on 5-ASA treatment using metagenomics, metatranscriptomics, and

metabolomics, researchers identified twelve previously uncharacterised microbial acetyltransferases that were upregulated in non-responders. *In vitro* assays confirmed that these enzymes acetylate 5-ASA into an inactive form, providing a mechanistic link between microbial metabolism and drug response.

In addition to metabolising drugs, some gut bacteria have been shown to actively transport and bioaccumulate drugs *in vitro* without modifying their chemical structure (**Figure 2**).[44] Duloxetine, an SNRI, bioaccumulates in diverse gut species, including many from the Firmicutes phylum (*Streptococcus salivarius, Clostridium bolteae, Clostridium saccharolyticum, Ruminococcus gnavus, Lactobacillus plantarum,* and *Lacticaseibacillus paracasei*), resulting in altered endogenous metabolism and secretion profiles. Duloxetine modulates *Caenorhabditis elegans* movement in a dose-dependent manner, and colonisation with the *Escherichia coli* IAI1 strain that is capable of bioaccumulating duloxetine attenuates this behaviour, highlighting that drug–microbiome interactions can impact behavioural outcomes.[44]

Finally, the gut microbiome can regulate host drug transporters, thus influencing pharmacokinetics. Differences in microbiome composition, such as between conventionally-raised and germ-free animals, alter the expression of the efflux transporter P-glycoprotein (P-gp/ABCB1),[45] which may contribute to pharmacokinetic variability for P-gp substrate drugs, including the SSRI sertraline and the antipsychotic risperidone. However, whether degradation, modification, bioaccumulation and/or altered transport of SSRIs or SNRIs impact anxiety or depression-like behaviours in mammalian model systems remains unexplored to date, defining a frontier of future research.

TOWARDS A HOLISTIC UNDERSTANDING OF DRUG–MICROBIOME INTERACTIONS

While microbial cell culture-based experiments offer rigorous insights into drug–microbiome interactions, these systems are unable to capture the physiology of an organism and its associated microbiome, with studies in freely behaving animals required to advance this research toward understanding effects on emotional behaviours. Recent *in vitro* findings have also revealed that reductions in drug levels do not necessarily indicate microbial metabolism.[20] Abiotic factors, including spontaneous degradation, ion suppression, surface adsorption, and bioaccumulation, can have strong effects on drug activity.

To ensure reproducible and clinically relevant results, it is important to test drug–microbiome interactions within their native host context, minimising artefacts introduced by culture conditions. Moreover, it is possible that long-term medication use can reshape the gut environment and microbiome composition, which then secondarily influences symptoms or treatment outcomes, though this concept remains hypothetical in the absence of empiric evidence. Disentangling these factors requires an integrated approach, combining multi-omics analyses of diverse human cohorts with rodent models or non-human primate models that are amenable to experimental approaches to define functional outcomes. Given that microbial bio-transformations largely fall within a defined set of reaction types, such as reduction, hydrolysis, decarboxylation, and dealkylation, identifying overarching principles governing these transformations may be feasible. Leveraging large-scale machine learning models trained on high-

resolution microbiome and metabolomics datasets could offer a powerful strategy to predict drug modifications and their downstream effects, ultimately guiding the design of more precise and effective therapeutic interventions.

As our understanding of drug–microbiome interactions becomes more refined, the development of predictive frameworks for drug efficacy and tolerability based on an individual's symptoms, lifestyle, medication history, and microbiome status will be increasingly feasible. Such tools could one day help tailor pharmacological treatments to maximise therapeutic benefit, ultimately advancing precision medicine. It is conceivable that gut microbiome variations explain inter-individual responses to numerous classes of oral drugs, beyond those for neuropsychiatric conditions, and potentially even injectables via microbiome modulation of immune profiles (e.g., immune checkpoint inhibitors)[46-48] and metabolic states (e.g., weight loss drugs).[49,50] Identifying microbiome-based markers that quantitatively predict variance in drug response in defined patient populations may streamline drug discovery and development, improve efficacy rates and response times, and reduce side effects.

References

1. Sender R et al. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533.

2. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448(7152):427-34.

3. Louis P et al. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol. 2014;12(10):661-72.

4. Qin J et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55-60.

5. Morais LH et al. The gut microbiota-brain axis in behaviour and brain disorders. Nat Rev Microbiol. 2021;19(4):241-55.

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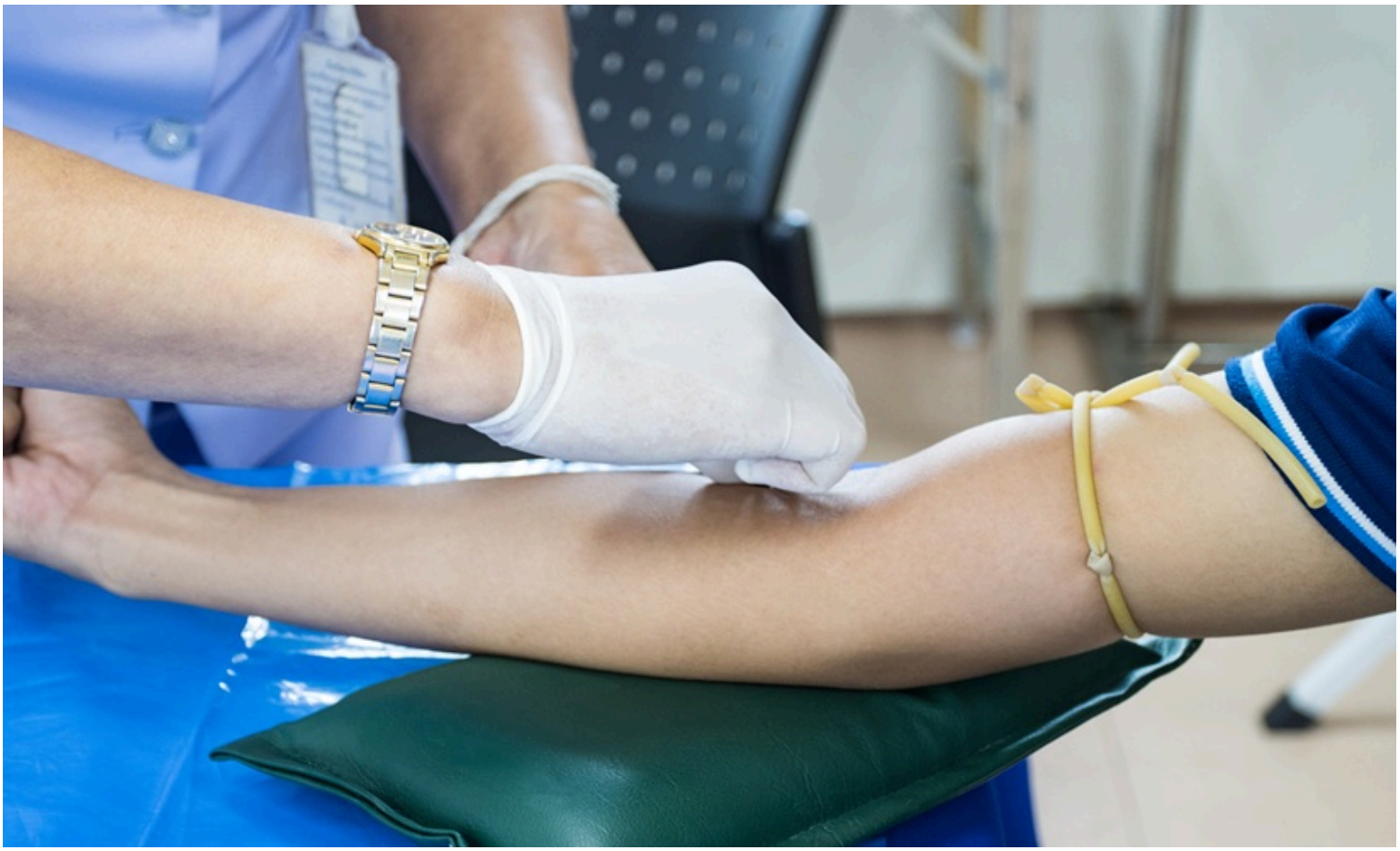

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SEÇÃO: ARTIGO

Suicidal ideation in mothers of asthmatic children and adolescents in a subspecialty outpatient practice

Ideação suicida em mães de crianças e adolescentes asmáticos em ambulatório especializado

Ideación suicida en madres de niños y adolescentes asmáticos en consulta externa de subespecialidad

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Abstract: We aimed to investigate prevalence and factors associated with Suicide ideation (SI) in mothers of asthmatic children. This cross-sectional study included 362 dyads of mothers and children with asthma aged 2 to 14 years who attended two pediatric outpatient clinics in Brazil. We assessed the presence of SI (Self-Report Questionnaire-20), the occurrence of stressful events and maternal social support. The prevalence of SI was 8.6%. Low maternal education, exposure to *serious illness*, and low perception of social support in its affective–social interaction dimension remained significantly associated with SI in the final model. Thus, life stressors, social support and low maternal education accounted for most of the variation in prevalence of maternal SI. There were no effects of child asthma severity on maternal SI in this study.

Keywords: suicidal ideation, mental health, maternal behavior, asthma

Resumo: Nosso objetivo foi investigar a prevalência e os fatores associados à ideação suicida (IS) em mães de crianças asmáticas. Este estudo transversal incluiu 362 díades de mães e crianças com asma de 2 a 14 anos em dois ambulatórios pediátricos no Brasil. Avaliamos a presença de IS (Self-Report Questionnaire-20), a ocorrência de eventos estressantes e o suporte social materno. A prevalência de IS materna foi de 8,6%. Escolaridade materna inferior a oito anos, doença materna grave e a baixa percepção de suporte social em sua dimensão afetivo-social permaneceram significativamente associadas à IS no modelo final. Portanto, eventos estressores maternos, suporte social e baixa escolaridade materna foram os responsáveis pela maior parte da variação na prevalência de IS materna. Não houve efeitos da gravidade da asma infantil na IS materna neste estudo.

Palavras-chave: ideação suicida, saúde mental, comportamento materno, asma

Resumen: Este estudio investigo la prevalencia y los factores asociados com ideación suicida (IS) en madres de niños asmáticos. Participaron 362 díadas de madres y niños con asma de 2 a 14 años en dos clínicas pediátricas ambulatorias en Brasil. Evaluamos la presencia de IS (Self-Report Questionnaire-20), la ocurrencia de eventos estresantes y el apoyo social materno. La prevalencia de IS materno fue del 8,6%. La educación materna de menos de ocho años, la enfermedad materna grave y la baja percepción de apoyo social en su dimensión afectivo-social se mantuvieron significativamente asociadas con el SI en el modelo final. Entonces, los eventos de estrés materno, el apoyo social y la baja educación materna explicaron la mayor parte de la variación en la prevalencia materna de IS. No hubo efectos de la gravedad del asma infantil en el IS materno en este estudio.

Palabras clave: ideación suicida, salud mental, conducta materna, asma

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Every year, over 800,000 people die from suicide worldwide (World Health Organization, 2014). Suicide is the 15th most common cause of death and accounts for 1.4% of all deaths globally; 75.5% of these deaths occur in developing countries (Cha et al., 2018; Turecki & Brent, 2016; World Health Organization, 2014, 2017). Suicidal behavior is a spectrum that includes suicidal ideation (SI), planning, attempt, and the action of committing suicide itself (World Health Organization, 2014). However, suicidal ideation (SI) inclusion in suicidal behavior is controversial because the factors associated with SI may differ from the factors underlying suicide attempt and suicide itself (Klonsky et al., 2016; Wetherall et al., 2018; World Health Organization, 2014). The SI prevalence was 9.2% in a multicenter study involving 17 countries. Studying SI and its determinants is important because up to 60% of the transitions to suicide planning and attempt can occur in the first year after suicidal thoughts are developed (Nock et al., 2008).

As SI can be an important predictor of death by suicide (Nock et al., 2008; World Health Organization, 2014), it is extremely important to identify SI as a topic for planning suicide prevention. Some theories regarding suicide and suicidal behavior are rooted in the ideation-to-action framework. These theories consider SI development and SI transition to suicide attempt as distinct processes (Joiner, 2005; Klonsky & May, 2015; Klonsky et al., 2017; O'Connor, 2011). The Three-Step Theory (3ST), for example, hypothesizes that: 1) SI results from the combination of pain (mainly psychological) and hopelessness; 2) among those who experience one or both, connectedness is a crucial protective factor against the escalating SI and 3) progression from ideation to attempts depends on dispositional, acquired, and practical contributors to the capacity to attempt suicide (Klonsky & May, 2015; Klonsky et al., 2017). Regarding the first and second steps of 3ST, stressful life events (SLE) may act as a trigger and social support as a protective factor on the escalating SI. In the first case, association between negative stressful situations and SI and behavior was generally consistent (Liu & Miller, 2014).

As caring for patients with chronic mental or physical illness can be a stressful event, a growing number of studies have investigated aspects of the caregiver's mental health, including SI, whose prevalence may range from 10.3 to 18% (Huang et al., 2018; Koyama et al., 2017; O'Dwyer et al., 2016; Park et al., 2013; Skeen et al., 2014). Studies revealed much heterogeneity, with SI prevalence depending on child's illness type and other factors associated with the caregiver, such as the presence of CMD, depression, and anxiety, social support, age, and associated chronic disease (Huang et al., 2018; O'Dwyer et al., 2016; Park et al., 2013; Skeen et al., 2014). Being single, female, and unemployed; having low perception of social support; and presenting a mental disorder have been frequently identified as factors for increased risk of SI among caregivers (Huang et al., 2018; O'Dwyer et al., 2016). In the particular case of children, studies evaluating the presence of suicidal thoughts in their caregivers, especially mothers (if we consider that they are the main caregivers in this age group), are lacking. (Lise et al., 2017).

Moreover, no studies have tested any type of socioeconomic and/or psychosocial model for SI in mothers of children with asthma, the most prevalent chronic disease in childhood. (Asher & Pearce, 2014; Global Initiative for Asthma, 2015) Thus, this study aims to investigate the socioeconomic and psychosocial factors that are associated with an increased prevalence of SI in mothers of asthmatic children in subspecialty outpatient practice. Since having a child with asthma can be a stressful event for the mother, we will consider the additional stress of severe asthma in the child as a determinant for SI in these mothers.

Methods

Participants

This study was conducted in two public pediatric pulmonology outpatient clinics that are reference for attendance of children and adolescents in the state of Alagoas, Brazil. Eligible participants were mothers of asthmatic children aged 2 to 14

years selected by convenience.

A total of 481 eligible mothers were invited to participate in the study. Once they agreed to participate and signed a consent form, a face-to-face interview was conducted in a private room before medical appointment. Seventeen mothers refused to participate, and 102 questionnaires were excluded due to inconsistencies in their completion or by noting that mothers were embarrassed to complete one or more items in the questionnaire.

Mother-child dyads included mainly male children, mothers with low education, and severe financial problems (see table 1 for detailed information on socio-demographic characteristics, maternal factors, and asthma severity in the sample).

Measurements

Maternal SI. Information about maternal SI was obtained through the question "Have you had thoughts about ending your life in the past 30 days?" from the Self Report Questionnaire (SRQ-20). This is a common mental disorder (CMD) screening questionnaire comprising 20 questions and dichotomous answers (yes/no) on symptoms over the previous 30 days and validated in Brazil (Harding et al., 1980; Mari & Williams, 1986). Participants were divided into groups of mothers with and without SI.

Maternal stressful life events (SLE). The occurrence of maternal stressful life events (SLE) in the previous 12 months was measured through nine close-ended questions about events or unpleasant situations taking place over the previous 12 months, with dichotomized answers in *yes* or *no* – exposed or non-exposed, respectively (Lopes & Faerstein, 2001). Each one of the nine events was evaluated as an isolated variable (serious illness, hospitalization, death of close family member, severe financial problems, change of residence, separation/divorce, physical aggression, mugging/robbery). This questionnaire showed good test-retest reliability, with most of the questions having a good stability when reported by adults in a previous study in Brazil (Lopes & Faerstein, 2001).

Maternal Social Support. Maternal social support was assessed using the Social Support Scale (Medical Outcomes Study Questions; MOS-SSS). The instrument consisted of 19 questions and answers on a five-item Likert scale ("never" – 1, "rarely" – 2, "sometimes" – 3, "almost always" – 4 and "always" – 5), validated for the Brazilian population (GRIEP et al., 2005). For the purposes of this study, the items were organized to cover three dimensions of social support: 1) affective–positive social interaction (7 items), 2) emotional–informational (8 items), and 3) material support (4 items) (Griep et al., 2005). The higher the score, the greater the perception of social support. The scores in each dimension were dichotomized at high and low, using the first distribution quartile as a cut-off point.

Support from relatives and friends. Support from relatives and friends was measured through the questions: 1) "How many relatives do you feel comfortable with and can talk about almost everything?" and 2) "How many friends do you feel comfortable with and can talk about almost everything?", also extracted from MOS-SSS mentioned above. Both variables were dichotomized based on presenting or not support from relatives or friends, at least one.

Covariates. Child's asthma severity was considered an adjustment variable, as this sample consists of mothers of asthmatic children. Child's gender, child's age, maternal age, maternal educational level, economic classification, and maternal smoking were considered as possible adjustment variables if they achieved significance ($p<0.05$) in the bivariate analysis for predictors of SI in the mothers. Asthma severity was defined based on the type of medication that was being used (Global Initiative for Asthma, 2015) and was categorized as mild or moderate to severe for analysis. For economic classification, the ABEP (*Associação Brasileira de Empresas de Pesquisa*) questionnaire was used, which categorizes economic classes as A, B, C, D, and E, in witch A was the highest and E was the lowest. For analysis, the economic classes were dichotomized in A/B/C

and D/E.

Procedures

This was a cross-sectional study conducted between June 2015 and December 2017 in two outpatient pediatric clinics in the State of Alagoas, Brazil. Participants included dyads of mothers and their respective asthmatic child aged 2 to 14 years. The data were collected through structured interviews with the mothers and by using data from patients' medical records.

After the Informed and direct consent was obtained from the mothers, questionnaires were applied. Application of the instrument (face-to-face), as well as the interview environment (waiting room) were used to minimize the gaps in filling in the questionnaires. However, the interviewees might have felt embarrassed with one or more items in the questionnaire. When this happened, we invalidated the instrument entirely and the participant was excluded from the research. When the mothers answered positively to the question "Have you had thoughts about ending your life in the past 30 days?", they were referred to the clinic's psychology service for follow-up. This assurance complies with items III, III.2 of the Guidelines and Regulatory Norms for Research Involving Humans, RESOLUTION No. 466, of the Brazilian NATIONAL HEALTH COUNCIL.

The Research Ethics Committee of the Federal University of Alagoas approved this study with the protocol number 1.091.863.

All the analyses were conducted using the STATA version 13.0 program. Association between the presence of maternal SI and categorical independent variables was analyzed by means of the qui square test. The variables that presented association at a level of $p \leq 0.05$ in the bivariate analysis with SI entered a multivariate regression model. Estimates by point (prevalence ratio; PR) and adjusted 95% confidence intervals (95% CIs) were calculated by using Poisson regression with robust variance in order to produce point and interval estimates that were lower than those obtained using logistic regression which would overestimate the associations for outcomes (Coutinho et al., 2008). A value of $p < 0.05$ was considered as statistically significant in the multivariate regression model.

To quantify the additional contribution of each group of independent variables to the variation observed in the dependent variable (maternal SI) explained by the model, such groups of interest variables were progressively added. Contribution with the addition of each group of variables to the model was measured by change in R^2. Successive models for association with maternal SI were: 1) socio-demographic factors; 2) Model 1 + perception of maternal social support; 3) Model 2 + maternal exposure to SLE in the previous year; 4) Model 3 + asthma severity.

Results

The maternal SI prevalence in the previous month was 8.6%. All mothers with SI also had evidence of common mental disorder (CMD), with eight or more positive answers to SRQ-20, a cut-off point defined in the Brazilian validation of the questionnaire (Mari & Williams, 1986). Half of the mothers in the sample had CMD. Almost half of the dyads belonged to economic classes D and E. Exposure to severe financial problems was the most frequently reported SLE in the previous year, followed by loss of a close relative (Table 1).

Table 1 – Socio-demographic characteristics, maternal factors and asthma severity of the sample (n=362)

Characteristics	N (%)
Maternal SI*	31 (8,6%)
Maternal CMD**	183 (50,55%)
Gender of the child, male	232 (64,09%)
Age of child (≤ 5 years)	161 (44,48%)
Asthma severity in the child (moderate / severe)	146 (40,33%)
Maternal age (> 35 years)	116 (32,04%)
Maternal education (less than eight years)	212 (58,56%)
Economic class (D/E)	175 (48,34%)
Maternal smoking	18 (4,97%)
Affective – positive social interaction support, low	82 (22,65%)
Emotional – informational support, low	91 (25,14%)
Material support, low	103 (28,45)
Relatives support (none)	64 (17,68%)
Friends support	166 (45,86%)
Maternal stressful life events (SLE) in the last year (2 or more)	190 (52,49%)
Serious illness	105 (29,01%)
Hospitalization	29 (8,01%)
Death of close family member	116 (32,04%)
Severe financial problems	206 (56,91%)
Forced change of residence	63 (17,40%)
Separation/divorce	50 (13,81%)
Mugging/robbery	39 (10,77%)
Physical aggression	17 (4,70%)
Discrimination	14 (3,87%)

* CMD: Common mental disease; **SI: Suicidal ideation

Bivariate Relationships between maternal SI, sociodemographic characteristics, maternal psychosocial factors, and Child's Asthma severity. Mothers with less than eight years of schooling and mothers belonging to economic classes D and E showed a positive association with SI (PR: 2,95; CI95%: 1,24 – 7,02 and PR: 2,24; CI95%: 1,09 – 4,63, respectively). Child's asthma severity was not associated with maternal SI report (Table 2).

Table 2 – Clinical and sociodemographic characteristics of the mother-child dyads, according to the presence of SI (n=362)

Characteristics	Without SI (n=331)	With SI (n=31)	PR	CI (95%)	p
Gender of the child, Male	213 (64.3%)	19 (61.3%)	0,89	0,44 – 1,77	0,73
Age of child, ≤ 5 years	149 (45.0%)	12 (38.7%)	0,79	0,39 – 1,58	0,50
Asthma severity in the child, Moderate / severe	131 (39.6%)	15 (48.4%)	1,39	0,71 – 2,72	0,34
Maternal age, > 35 years	105 (31.7%)	11 (35.5%)	1,17	0,58 – 2,35	0,67
Maternal education, Less than eight years	187 (56.5%)	25 (80.6%)	2,95	1,24 – 7,02	0,01*
Economic class (*ABEP*), D/E	154 (46.5%)	21 (67.7%)	2,24	1,09 – 4,63	0,03*
Maternal smoking, Yes	16 (4.8%)	2 (6.4%)	1,32	0,34 – 5,10	0,69

* $p < 0,05$

* ABEP: Associação Brasileira de Empresas de Pesquisa

Among the maternal psychosocial factors, perception of low social support in its three dimensions and exposure to most stressors in the previous year (serious illness, hospitalization, separation/divorce, and being victim of physical aggression and discrimination) were significantly associated with maternal SI (Table 3). Interpersonal support provided by relatives was also inversely associated with maternal SI.

Table 3 – Maternal psychosocial characteristics, according to the presence of SI (n=362)

Characteristics	Without SI (n=331)	With SI (n=31)	PR	CI (95%)	P
Serious illness	90 (27.2%)	15 (48.4%)	2,29	1,18 – 4,47	0,01*
Hospitalization	21 (6.3%)	8 (25.8%)	3,99	1,96 – 8,13	<0,01*
Death of close family member	103 (31.1%)	13 (41.9%)	1,53	0,78 – 3,02	0,22
Severe financial problems	184 (55.6%)	22 (71.0%)	1,85	0,88 – 3,91	0,11
Forced change of residence	58 (17.5%)	5 (16.1%)	0,91	0,36 – 2,29	0,84
Separation/divorce	41 (14.4%)	9 (29.0%)	2,55	1,25 – 5,23	0,01*
Mugging/robbery	34 (10.3%)	5 (16.1%)	1,59	0,65 – 3,91	0,31
Physical aggression	11 (3.3%)	6 (19.3%)	4,87	2,31 – 10,28	<0,01*
Discrimination	10 (3.0%)	4 (12.9%)	3,68	1,49 – 9,10	0,01*
Low Affective – positive social interaction support	62 (18.7%)	20 (64.5%)	6,21	3,10 – 12,43	<0,01*
Low Emotional – informational support	78 (23.6%)	13 (41.9%)	2,15	1,10 – 4,22	0,02*
Low Material support	88 (26.6%)	15 (48.4%)	2,36	1,21 – 4,59	0,01*
No support from relatives	53 (16.0%)	11 (35.5%)	2,56	1,29 – 5,08	0,01*
No support from Friends	151 (45.6%)	15 (48.4%)	1,11	0,56 – 2,17	0,77

* $p < 0,05$

Maternal SI, Stressors, Social Support and Child's Asthma severity: a series of Multivariate Models. To predict the dependent variable maternal SI, we estimated a series of regression models to identify the independent contributions of socio-demographic factors, social support, life stressors and childhood asthma severity to maternal SI. The variables that presented association at a level of $p < 0.05$ with SI entered the multivariate regression model. Although asthma severity was not associated with maternal SI in the bivariate analysis, we added this variable to the model to identify a possible strengthening or buffering effect of it on the other variables. In this multivariate model, we accounted for elements of the socio-demographic factors of mother-child dyads first, describing the relationships of social support and stressors to the mother's SI before we incorporated the additional stress of child's asthma severity (Table 4). Support from relatives and perception of social support added 16% of explanation to the SI model in this study measured by change in R^2. Thus, social support explained a considerable amount of additional variation in maternal SI, over and above socio-demographics factors. The included SLE added 7% to the explanation provided by socio-demographic factors and social support. Inclusion of asthma

severity did not explain additional variation in the cumulative model of maternal SI to the model, as observed by unaltered R^2. Maternal exposure to severe illness and the low social support in their affective–social interaction dimension remained significantly associated with SI in the final model, even with the addition of child's asthma severity to the model. The complete model accounted for 27% of maternal SI in this sample.

Table 4 – Multivariate regression model for SI asthmatic children and adolescents' mothers

SI	Model 1 socio-demographic factors (R^2 0,04)	Model 2 (Model 1 + perception of maternal social support) (R^2 0,20; Change in R^2:0,16)	Model 3 (Model 2 + maternal exposure to SLE in the previous year) (R^2 0,27; Change in R^2:0,07)	Model 4 (Model 3 + asthma severity) (R^2 0,27; Change in R^2:0,00)
	PR (CI 95%)	PR (CI 95%)	PR (CI 95%)	PR (CI 95%)
Economic classification (D/E)	1.36 (0.56 – 3.29)	1.18 (0.54 – 2.60)	1,03 (0.43 – 2.51)	1.03 (0.40 – 2.66)
Maternal educational level < 8 years of schooling	2.85 (0.96 – 8.44)	2.51 (0.97 – 6.52)	2,59 (1.05 – 6.38)*	2.59 (1.04 – 6.47)*
Low Affective – positive social interaction support		6.43 (2.37 – 17.46)*	6.86 (2.66 – 17.71)*	6.86 (2.67 – 17.65)*
Low Emotional – informational support		1.08 (0.49 – 2.38)	1.10 (0.54 – 2.22)	1.10 (0.53 – 2.27)
Low Material support		0.98 (0.44 – 2.18)	0.73 (0.29 – 1.80)	0.73 (0.30 – 1.79)
No support from relatives		2.09 (0.99 – 4.42)	2.05 (0.94 – 4.48)	2.05 (0.91 – 4.64)
Serious illness			3.25 (1.27 – 8.27)*	3.24 (1.25 – 8.44)*
Hospitalization			1.02 (0.36 – 2.87)	1.02 (0.36 – 2.93)
Separation/divorce			1.11 (0.45 – 2.76)	1.11 (0.45 – 2.75)
Physical aggression			2.61 (0.89 – 7.65)	2.62 (0.83 – 8.25)
Discrimination			1.66 (0.74 – 3.74)	1.66 (0.69 – 3.99)
Asthma severity				1.00 (0.45 – 2.30)

* $p < 0,05$

Discussion

This study including mothers of asthmatic children in a subspecialty outpatient practice regarding suicidal thoughts in the previous month found a SI prevalence of 8.6%, which was similar to that found in a previous multicenter study – 9.2% (Nock et al., 2008). Thus, there does not seem to exist a higher prevalence of SI in this population. SI prevalence can differ from one study to another depending on the evaluation method (response to only one question or a specific questionnaire, population characteristics, and assessment time – if ever in life, the previous month, or the previous year). For example, a study involving young adults in Scotland revealed up to 23% of suicidal thoughts at one time in life and 10.6% in the previous 12 months (O'Connor et al., 2018). In Brazil, a study carried out with pregnant women and using a methodology like the methodology described here found SI prevalence of 6.3% (Huang et al., 2012).

Based on the assumption that context matters, we built the mother's social context by creating a model of demographics, social support and life stress that served as a backdrop for the additional stress of having a child with severe

asthma. By looking further into the model, we found that demographics mattered somewhat, but the lack of social support and experience of life stressors explained more of the presence of maternal SI. Moreover, the child's actual asthma severity had not a relationship to the mother's SI and did not make an additional contribution to the relationship between the psychosocial variables and maternal SI.

Different from previous studies evaluating the presence of SI in caregivers of individuals with chronic diseases such as HIV, chronic kidney disease, cerebrovascular disease, mental disorders, and cancer (Huang et al., 2018; Park et al., 2013; Skeen et al., 2014), we assessed whether the severity of the disease was associated with the presence of SI. We observed a lack of association between disease severity in child and the presence of maternal SI, including child's asthma severity to the multivariate analysis model. Although prospective studies with a larger number of subjects should confirm or not this lack of association, it seems that having a child with severe asthma *per se* may not be causally related to maternal SI. Asthma severity is a possible stressor, but other events related to interaction with the environment and social support may exert a greater influence on suicidal thinking, possibly related to the individual's inherent feeling of non-belonging and non-connectivity regardless of the amount of care that is required.

In line with the 3ST theory, which considers that events that cause pain and hopelessness trigger IS, we identified in our study that the SLE serious illness increased the risk of SI in mothers of children with asthma. In addition, low social support on its affective and social interaction dimension remained associated with SI in an adjusted analysis, strengthening the idea contained in the 3ST hypothesizing that connectedness may act as a protective factor against progression of SI. Thus, in mothers of asthmatic children, the event serious illness (a trigger) and the lack of affective and social interaction support (the connectedness protective factor) are important determinants of suicidal thinking in mothers caring for children with a chronic condition.

Several factors, mainly psychosocial factors, are associated with SI in caregivers including CMD, depression, anxiety, low perception of social support, exposure to stressful events, low quality of life, and coping strategies (Huang et al., 2018; O'Dwyer et al., 2016; Park et al., 2013; Skeen et al., 2014). For SLE, studies involving caregivers are lacking. The most common SLE identified in a British study involving 1066 patients with psychological morbidity and SI were loss of family or friend, interpersonal conflicts, severe illness, financial crisis, and interpersonal violence (McFeeters et al., 2015). In an epidemiological study conducted in the United States involving 34,653 adults with major depressive disorder, SI was associated with stressors loss or victimization, problems with interpersonal relationships, serious problems with neighbors, friends, or relatives, and financial difficulties (Wang et al., 2015). Although the above-mentioned stressors were associated with SI in other studies, in the present study, only the event severe illness remained associated with SI after multivariate analysis.

In relation to social support, previous studies shows that it exerts an effect on SI among adolescents by mediating its relationship with stressors (Kang et al., 2017). Further, the lack of support from relatives has also been associated (in the unadjusted analysis) with the presence of SI in caregivers of patients with physical and mental illness in a tertiary hospital in Taiwan (Huang et al., 2018). The present study adds that perceived lack of social support in their affective–social interaction dimension was significantly associated with SI in mothers of asthmatic children, in an adjusted model.

Among the socio-demographic factors associated with SI occurrence, only the maternal schooling factor remained statistically significant after adjusted analysis. A study in Korea evaluated the risk factors for SI in migraine patients and, through logistic regression analysis, found that patients with SI were more likely to have a low educational level - measured in years of study - as compared to patients without SI (Kim & Park,

2014). Among caregivers of cancer patients, being female, single, and unemployed were also socio-demographic factors associated with higher risk of SI (Park et al., 2013).

This study had some limitations. First, because of its cross-sectional design, we were not able to determine cause and effect relationship between SI and the considered factors. Because both the exposure and outcome are determined at the same time, no temporality between these variables can be inferred. However, the present study was useful to provide a snapshot of the association between SI and maternal psychosocial at one point in time whose direction of effect can be better indicated in a prospective study. Second, some possible confounding factors may have affected self-reporting of SI and attempts, including educational level, understanding and interpretation of the questionnaire, and respondent's willingness to disclose this information (World Health Organization, 2014). Application of the instrument (face-to-face), as well as the interview environment (waiting room) were used to minimize the gaps in filling in the questionnaires. However, the interviewees may have felt embarrassed, which may have altered their responses and consequently underestimated the results of the questions related to the stressor physical aggression event and the presence of SI for example. The researchers in relation to the risks of constraints offered guarantee of data confidentiality and withdrawal from the study without consequences for the treatment of the child to the research participants. Finally, there is no questions about frequency, intensity, or duration of SI in the suicide item of the SRQ-20, thus limiting its ability to assess the severity of suicidality.

Despite these concerns, the present study has many important strengths, such as demonstrating a model where the psychosocial context explains much more IS in mothers of asthmatic children than the severity of the disease in the child. Moreover, it raises the possibility of identifying maternal SI and associated factors in a routine outpatient child consultation by means of a simplified instrument with rapid application (20-30 minutes). There was no need for the interviewers to go through complex training. The instrument could be useful mainly in the context of primary healthcare, could be applied in an outpatient waiting room, is easily accessible, and has low cost for the health system. Once the risk is identified, the caregiver should be referred to specialized care for appropriate diagnosis and treatment. The importance of identifying SI and associated factors could enable early intervention and prevention or block the process leading from ideation to suicidal behavior through active search in an interview with mothers. In addition, providing support to the mother will probably improve their children's asthma status.

Conclusions

The SI prevalence in asthmatic children's mothers was the same as in the general population. Previously described psychosocial factors, as maternal education, exposure to stressors (in this case, serious illness) and low perception of social support in their affective–social interaction was also significantly associated with SI in mothers of asthmatic children. Our results points to the lack of association between severity of disease in children and SI in their mothers. In general, the presence of SI is better explained by the experience of life stressors and low perception of social support. Finally, the current study suggests that it is possible to identify maternal SI and associated factors with the aid of a simplified instrument during a routine visit to a child outpatient unit.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

Asher, I., & Pearce, N. (2014). Global burden of asthma among children. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*, *18*(11), 1269–78. https://doi.org/10.5588/ijtld.14.0170

Cha, C., Franz, P., Guzmán, E., Glenn, C., Kleiman, E., Nock, M. (2018). Annual Research Review: Suicide among youth – epidemiology, (potential) etiology, and treatment. *Journal of Child Psychology and Psychiatry*, *59*(4), 460-482. https://doi.org/ 10.1111/jcpp.12831

Coutinho, L., Scazufca, M., Menezes, P. (2008). Métodos para estimar razão de prevalência em estudos de corte transversal. *Revista de Saúde Pública*, *42*(6), 992–998. https://doi.org/10.1590/S0034-89102008000600003

Global Initiative For Asthma. (2015). *Global strategy for asthma management and prevention*. GINA report. http://ginasthma.org/wp-content/uploads/2016/01/GINA_Report_2015_Aug11-1.pdf

Griep, R., Chor, D., Faerstein, E., Werneck, G., Lopes, C. (2005). [Construct validity of the Medical Outcomes Study's social support scale adapted to Portuguese in the Pró-Saúde Study]. *Cadernos de saude publica*, *21*(3), 703-14. https://doi.org/10.1590/S0102-311X2005000300004

Harding, T., Arango, M., Baltazar, J., Climent, C., Ibrahim, H., Ladrido-Ignacio, L., Murthy, R., Wig, N. (1980). Mental disorders in primary health care: a study of their frequency and diagnosis in four developing countries. *Psychological medicine*, *10*(2), 231–41. https://doi.org/10.1017/s0033291700043993

Huang, H., Faisal-Cury, A., Chan, Y., Tabb, K., Katon, W., Menezes, P. (2012). Suicidal ideation during pregnancy: prevalence and associated factors among low-income women in São Paulo, Brazil. *Archives of Women's Mental Health*, *15*(2), 135-138. https://doi.org/10.1007/s00737-012-0263-5

Huang, Y., Hsu, S., Hung, C., Wang, L., Chong, M. (2018). Mental health of caregivers of individuals with disabilities: Relation to Suicidal Ideation. *Comprehensive psychiatry*, *81*, 22-27. https://doi.org/10.1016/j.comppsych.2017.11.003

Joiner, T. E. (2005). *Why People Die By Suicide*. Harvard Univ. Press.

Kang, B., Kang, J., Park, H., Cho, Y., Hur, Y., Sim, W., Byeon, G., Kim, K.(2017). The Mediating Role of Parental Support in the Relationship between Life Stress and Suicidal Ideation among Middle School Students. *Korean journal of family medicine*, *38*(4), 213-219. https://doi.org/10.4082/kjfm.2017.38.4.213

Kim, S.-Y., & Park, S.-P. (2014). Suicidal ideation and risk factors in Korean migraine patients. *Journal of Clinical Neuroscience*, *21*(10), 1699-1704. https://doi.org/10.1016/j.jocn.2014.03.016

Klonsky, E. D., & May, A. M. (2015). The Three-Step Theory (3ST): A New Theory of Suicide Rooted in the "Ideation-to-Action" Framework. *International Journal of Cognitive Therapy*, *8*(2), 114-129. https://www2.psych.ubc.ca/~klonsky/publications/3ST.pdf

Klonsky, E., May, A., Saffer, B. (2016). Suicide, Suicide Attempts, and Suicidal Ideation. *Annual Review of Clinical Psychology*, *12*(1), 307-330. https://doi.org/10.1146/annurev-clinpsy-021815-093204

Klonsky, E., Qiu, T., Saffer, B. (2017). Recent advances in differentiating suicide attempters from suicide ideators. *Current opinion in psychiatry*, 30(1), 15-20. https://doi.org/10.1097/YCO.0000000000000294

Koyama, A., Matsushita, M., Hashimoto, M., Fujise, N., Ishikawa, T., Tanaka, H., Hatada, Y., Miyagawa, Y., Hotta, M., Ikeda, M. (2017). Mental health among younger and older caregivers of dementia patients. *Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society*, *17*(2), 108-114. https://doi.org/10.1111/psyg.12200

Lise, F., Schwartz E., Milbrath, V., Santos, B., Feijó, A., Garcia, R. (2017). Criança Em Tratamento Conservador Renal: Experiências Das Cuidadoras Familiares. *Texto & Contexto - Enfermagem*, *26*(3), e1110016. https://doi.org/10.1590/0104-07072017001110016

Liu, R. T., & Miller, I. (2014). Life events and suicidal ideation and behavior: A systematic review. *Clinical Psychology Review*, *34*(3), 181–192. https://doi.org/10.1016/j.cpr.2014.01.006

Lopes, C., & Faerstein, E. (2001). Confiabilidade do relato de eventos de vida estressantes em um questionário autopreenchido: Estudo Pró-Saúde. *Revista Brasileira de Psiquiatria*, *23*(3), 126-133. https://doi.org/10.1590/S1516-44462001000300004.

Mari, J., & Williams, P. (1986). A validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of Sao Paulo. *British Journal of Psychiatry*, *148*(1), 23-26. https://doi.org/10.1192/bjp.148.1.23

Mcfeeters, D., Boyda, D., & O'neill, S. (2015). Patterns of stressful life events: distinguishing suicide ideators from suicide attempters. *Journal of affective disorders*, *175*, 192-8. https://doi.org/10.1016/j.jad.2014.12.034

Nock, M., Borges, G., Bromet, E., Alonso, J., Angermeyer, M., Beautrais, A., Bruffaerts, R., Chiu, W., de Girolamo, G., Gluzman, S., de Graaf, R., Gureje, O., Haro, J., Huang, Y., Karam, E., Kessler, R., Lepine, J., Levinson, D., Medina-Mora, M., Ono, Y., ... Williams, D. (2008). Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *British Journal of Psychiatry*, *192*(2), 98-105. https://doi.org/10.1192/bjp.bp.107.040113

O'connor, R. C. (2011). Towards an Integrated Motivational-Volitional Model of Suicidal Behaviour. In R. C. O'Connor, S. Platt, & J. Gordon (Eds.), International handbook of suicide prevention: Research, policy and practice (pp. 181–198). Wiley Blackwell. https://doi.org/10.1002/9781119998556.ch11

O'Connor, R., Wetherall, K., Cleare, S., Eschle, S., Drummond, J., Ferguson, E., O'Connor, D., O'Carroll, R. (2018). Suicide attempts and non-suicidal self-harm: national prevalence study of young adults. *BJPsych open*, *4*(3), 142-148. https://doi.org/10.1192/bjo.2018.14

O'Dwyer, S., Moyle, W., Zimmer-Gembeck, M., & De Leo, D. (2016). Suicidal ideation in family carers of people with dementia. *Aging & mental health*, *20*(2), 222–30. https://doi.org/10.1080/13607863.2015.1063109

Park, B., Kim, S., Shin, J., Sanson-Fisher, R., Shin, D., Cho, J., Park, J. (2013). Suicidal Ideation and Suicide Attempts in Anxious or Depressed Family Caregivers of Patients with Cancer: A Nationwide Survey in Korea. *PLoS ONE*, *8*(4), e60230. https://doi.org/10.1371/journal.pone.0060230

Skeen, S., Tomlinson, M., Macedo, A., Croome, N., Sherr, L. (2014). Mental health of carers of children affected by HIV attending community-based programmes in South Africa and Malawi. *AIDS care*, *26*(Suppl 1), S11-20. https://doi.org/10.1080/09540121.2014.906559

Turecki, G., & Brent, D. A. (2016). Suicide and suicidal behaviour. *Lancet*, *387*(10024), 1227–39.

Wang, Y., Sareen, J., Afifi, T., Bolton, S., Johnson, E., Bolton, J. (2015). A population-based longitudinal study of recent stressful life events as risk factors for suicidal behavior in major depressive disorder. *Archives of suicide research : official journal of the International Academy for Suicide Research*, *19*(2), 202–17. https://doi.org/10.1080/13811118.2014.957448

Wetherall, K., Cleare, S., Eschle, S., Ferguson, E., O'Connor, D., O'Carroll, R., & O'Connor, R. From ideation to action: Differentiating between those who think about suicide and those who attempt suicide in a national study of young adults. *Journal of Affective Disorders*, *241*(0), 475-483, 2018. https://doi.org/10.1016/j.jad.2018.07.074

World Health Organization. (2014). Preventing suicide: a global imperative. WHO.

World Health Organization. (2015). Disease and injury country mortality estimates, 2000–2015 [Data files]. Acessado em 23 set. 2017, de http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

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