Sex Disparities in Mortality Outcomes among COPD Patients Awaiting Lung Transplantation: A Comprehensive Analysis

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ABSTRACT **Background:** Lung transplantation (LT) is a viable option for end-stage chronic obstructive pulmonary disease (COPD) patients when conventional treatments fail. However, sex disparities in mortality outcomes among COPD patients awaiting LT remain understudied. LT waiting lists are generally shorter in Western countries compared to Israel.

Objectives: To evaluate sex-specific differences in mortality and co-morbidities among COPD patients awaiting lung transplantation, to identify key risk factors influencing survival.

Methods: We assessed associations between sex, co-morbidities, exacerbations, and mortality using Cox regression models, adjusting for confounders. Survival curves for lung transplant candidates were stratified by sex using Fine and Gray models.

Results: We identified 385 COPD patients listed for LT at Rabin Medical Center. Females exhibited higher rates of asthma ($P = 0.008$), anxiety ($P = 0.005$), and depression ($P = 0.002$); males were more frequently diagnosed with ischemic heart disease (26.5% vs. 10.83%, $P = 0.001$) and had a higher lung transplant rate (24.9% vs. 15%, $P = 0.029$). Multivariate analysis revealed that female sex (hazard ratio [HR] 1.55, 95% confidence interval [95%CI] 1.06–2.29, $P = 0.025$), older age (HR 1.02, 95%CI 1.002–1.054, $P = 0.035$), ischemic heart disease (HR 1.69, 95%CI 1.12–2.48, $P = 0.011$), and depression (HR 1.81, 95%CI 1.15–2.83, $P < 0.01$) were significantly associated with increased mortality. Females showed higher 1-year mortality rates than males (40.3% vs. 29.8%, $P < 0.001$).

Conclusions: Female sex is a significant risk factor for increased mortality among COPD patients awaiting LT, likely due to a higher burden of co-morbidities.

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KEY WORDS: chronic obstructive pulmonary disease (COPD), lung transplant candidates, sex disparities

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality globally [1]. For patients with end-stage COPD, lung transplantation (LT) is considered when other treatments have failed or are unsuitable [2]. Historically, COPD has been the leading indication for LT, with 36% of all lung transplants worldwide performed for COPD patients [3].

Due to the limited availability of donor lungs, many patients remain on long waiting lists, and some die while waiting. A key determinant of mortality on the waiting list is the presence of adverse prognostic factors. To improve organ allocation, the Thoracic Organ Transplantation Committee introduced a composite allocation score (CAS), which prioritizes patients by balancing waitlist mortality and post-transplant survival rather than simply based on waitlist duration [4].

Research on sex differences in mortality among end-stage COPD patients is limited, with most studies focusing on broader stages of the disease [5]. Israel presents a unique case, as lung transplantation wait times are significantly longer than in countries like the United States, where most candidates (61.4%) spend fewer than 90 days on the waiting list [6]. Prolonged waiting times in Israel may be due to the low availability of lung donors and the previous lung allocation score (LAS) system, which gave lower priority to COPD patients compared to those with interstitial lung disease. This extended wait provides an opportunity to assess survival rates among end-stage COPD patients.

In this study, we investigated sex differences in survival outcomes among end-stage COPD patients awaiting lung transplantation.

PATIENTS AND METHODS

STUDY POPULATION AND DESIGN

This study was designed as a retrospective investigation of patients treated at Israel's National Center for Lung Transplantation, which is located on the Beilinson campus of Rabin Medical Center. The center opened in 1996. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee.

We included COPD patients who were placed on the lung transplantation waiting list between January 2013 and January 2023. Patients who underwent retransplantation were excluded from the cohort. Lung transplant candidate selection followed international guidelines for lung transplantation [5].

For analysis, demographics, clinical data, lung function tests (LFT), right heart catheterization (RHC) data, and all-cause mortality were collected and analyzed. Patients were stratified by sex for comparative analysis.

FOLLOW-UP PROTOCOL

Lung transplant candidates were routinely registered and followed according to the International Society for Heart and Lung Transplantation guidelines [5]. We examined patient history, number of exacerbations during the first year, co-morbidities, LFT, and RHC for each patient before placement on the transplantation waiting list. The following parameters of LFT were obtained: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, total lung capacity (TLC), residual volume (RV), six-minute walk distance (6MWTD) and diffusing lung capacity for carbon monoxide (DLCO). The following RHC data were collected: mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), cardiac output (CO), and pulmonary vascular resistance (PVR). The lung transplant candidates were evaluated in the ambulatory clinic every 3–4 months, on average. More frequent visits were scheduled according to clinical needs. Follow-up included a detailed medical interview, physical examination, and LFT. Computed tomography of the chest and echocardiographic examinations were performed routinely every 12 months. The primary study outcome was all-cause mortality following placement on the transplantation waiting list. Vital status was registered based on information from electronic medical records and the registry of the Ministry of Internal Affairs. The follow-up period ended in February 2024.

STATISTICAL ANALYSIS

The results are expressed as the means and standard deviations for quantitative data and as numbers (percentages) for qualitative data. We used the chi-square test to compare categorical variables and ANOVA to compare continuous variables. Statistical comparisons were performed between the data obtained for the study groups. Univariable and multivariable Fine and Gray competing-risks regression models were used to evaluate predictors of mortality among wait-listed lung transplant candidates, with lung transplantation treated as the competing event. Results are reported as subdistribution hazard ratios with 95% confidence intervals. Cumulative incidence curves for mortality, stratified according to sex, were derived from the Fine and Gray model. *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

BASELINE CHARACTERISTICS

Table 1 presents a comparison of the baseline characteristics of 381 lung transplant candidates, divided by sex: 120 females and 261 males. The mean age for the entire cohort was 61.48 ± 7.52 years, with males comprising 68.5% of the sample. Females had significantly higher rates of asthma ($P = 0.008$), anxiety ($P = 0.005$), and depression ($P = 0.022$, as well as higher total lung capacity (TLC, $P < 0.001$), shorter 6MWTD ($P = 0.04$), lower CO ($P < 0.001$), and greater PVR ($P = 0.004$). In contrast, males had a significantly higher prevalence of ischemic heart disease compared to females (26.5% vs. 10.83%, $P = 0.001$). In addition, the proportion of lung transplants was greater in males than in females (24.9% vs. 15%, $P = 0.029$).

UNIVARIATE ANALYSIS

Table 2 shows the univariate analysis of mortality on the lung waiting list. According to the univariate analysis, the following variables were significantly associated with mortality: female sex (hazard ratio [HR] 1.53, 95%confidence interval [95%CI] 1.07–2.22, $P = 0.01$), older age (HR 1.03, 95%CI 1.01–1.05, $P = 0.01$), shorter time from listing to first exacerbation (HR 1.01 95%CI 1.01–1.02, $P < 0.001$), total number of exacerbations per year (HR 1.09, 95%CI 1.01–1.18, $P = 0.03$), having ischemic heart disease (1.53, 95%CI 1.05–2.23, $P = 0.02$), having cerebral vascular accident (HR 2.20, 95%CI 1.08–4.67,

Table 1. Baseline characteristics of the study population; waitlisted lung transplant candidates with COPD were stratified according to sex

Variable	Entire sample (n=381)	Male (n= 261)	Female (n=120)	*P*-value
Age in years	61.48 ± 7.52	61.61 ± 7.78	61.21 ± 6.94	0.21
Body mass index (kg/m^2)	24.36 ± 5.77	24.15 ± 5.71	24.79 ± 5.92	0.38
Number of patients who underwent lung transplant, n (%)	83 (21.78%)	65 (24.9%)	18 (15%)	**0.029**
Time to first COPD exacerbation post-listing in days	164.25 ± 313.9	171.55 ± 368.65	149.65 ± 131.4	**0.001**
hospitalization duration in first year post-listing in days	5.68 ± 12.34	5.03 ± 10.61	7.11 ± 15.43	0.46
Total number of exacerbations	0.94 ± 1.74	0.88 ± 1.6	1.08 ± 2.02	0.58
Co-morbid conditions				
Hypertension, n (%)	124 (32.55%)	90 (34.48%)	34 (28.33%)	0.39
Diabetes mellitus, n (%)	89 (23.36%)	68 (26.05%)	21 (17.5%)	0.14
Ischemic heart disease, n (%)	81 (21.26%)	68 (26.05%)	13 (10.83%)	**0.001**
Pulmonary embolism, n (%)	9 (2.36%)	6 (2.3%)	3 (2.5%)	1
Cerebral vascular accident, n (%)	9 (2.36%)	8 (3.07%)	1 (0.83%)	0.287
Asthma, n (%)	57 (14.96%)	30 (11.49%)	27 (22.5%)	**0.008**
Anxiety, n (%)	28 (7.35%)	12 (4.6%)	16 (13.33%)	**0.005**
Depression, n (%)	60 (15.75%)	33 (12.64%)	27 (22.5%)	**0.022**
Lung function test				
FEV1 (% of predicted value)	28.22 ± 13.81	28.31 ± 14.92	28.03 ± 1.11	0.37
FVC (% of predicted value)	54.4 ± 17.16	53.91 ± 17.59	55.37 ± 16.3	0.34
TLC (% of predicted value)	118.53 ± 28.87	114.14 ± 28.31	126.93 ± 28.2	**< 0.001**
RV (% of predicted value)	230.56 ± 75.44	225.48 ± 77.64	239.84 ± 72.74	0.09
DLCO (% of predicted value)	32.36 ± 14.9	33.35 ± 15.47	30.33 ± 13.5	0.09
6MWD (meters)	230.07 ± 121.02	244.09 ± 128.22	203.13 ± 101.44	**0.04**
Right heart catheterization data				
CO (L/min)	4.29 ± 1.19	4.49 ± 1.17	3.9 ± 1.13	**< 0.001**
CI (L/min/m^2)	2.41 ± 0.59	2.42 ± 0.55	2.38 ± 0.67	0.23
PCWP (mmHg)	12.05 ± 6.38	12.03 ± 6.45	12.09 ± 6.27	0.92
MPAP (mmHg)	25.76 ± 9.68	26.02 ± 10.22	25.21 ± 8.45	0.96
PVR (WU)	6.56 ± 26.82	6.46 ± 28.07	6.76 ± 24.2	**0.004**

Data are presented as means ± standard deviations or numbers (percentages) of presented cases
*Bold signifies *P*-value of ≤ 0.05
95%CI = 95% confidence interval, 6MWD = six-minute walk distance, CO = cardiac output, CI = cardiac index, COPD = chronic obstructive pulmonary disease, DLCO = diffusing lung capacity for carbon monoxide, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, HR = hazard ratio, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistant, RV = residual volume, TLC = total lung, WU = wood units capacity

P = 0.03), having depression (HR 1.69, 95%CI 1.11–2.58, *P* = 0.013), and higher MPAP (HR 1.02, 95%CI 1.00–1.04, *P* = 0.04). The following variables were significantly associated with survival higher: FVC (HR 0.98, 95%CI 0.97–1.00, *P* = 0.04), higher DLCO (HR 0.97, 95%CI 0.96–0.99, *P* < 0.009), and higher 6MWD (HR 0.99, 95%CI 0.99–1.00, *P* = 0.02).

MULTIVARIATE ANALYSIS

We conducted multivariate logistic regressions for the re-evaluation of sex, age, cerebral vascular heart disease, ischemic heart disease, and depression for mortality [Table 3]. Female sex (HR 1.55 95%CI 1.05–2.29, *P* = 0.02), advanced age (HR 1.02, 95%CI 1.002–1.054, *P* = 0.03), ischemic heart disease (HR 1.69 95%CI 1.12–2.48, *P* =

Table 2. Univariate analysis for prognostic factors for mortality in lung transplantation waitlist patients with COPD

Variable	HR	95%CI	*P*-value
Female sex	1.53	1.07–2.22	**0.01**
Age	1.03	1.01–1.05	**0.01**
Body mass index (kg/m^2)	0.976	0.92–1.02	0.33
Time to first exacerbation post-listing	1.01	1.01–1.02	0.001
Hospitalization duration in first year post-listing	1.01	1.01–1.02	**< 0.0001**
Total number of exacerbations	1.09	1.01–1.18	**0.03**
Co-morbid conditions			
Hypertension	1.002	0.69–1.44	0.99
Diabetes mellitus	0.91	0.61–1.35	0.66
Ischemic heart disease	1.53	1.05–2.23	**0.02**
Pulmonary embolism	1.08	0.30–3.90	0.89
Cerebral vascular accident	2.20	1.08–4.67	**0.03**
Asthma	0.60	0.30–1.10	0.09
Anxiety	1.43	0.79–2.57	0.22
Depression	1.69	1.11–2.58	**0.01**
Lung function test			
FEV1	0.99	0.97–1.00	0.36
FVC	0.98	0.97–1.00	**0.04**
TLC (% of predicted value)	0.9	0.9–1.006	0.77
RV (% of predicted value)	1	0.99–1.003	0.96
DLCO (% of predicted value)	0.97	0.96–0.99	**0.009**
6MWD	0.99	0.99–1.00	**0.02**
Right heart catheterization data			
CO (L/min)	1.005	0.79–1.27	0.96
CI (L/min/m^2)	1.28	0.87–1.89	0.2
PCWP (mmHg)	0.99	0.96–1.03	0.83
MPAP (mmHg)	1.02	1.00–1.04	**0.04**
PVR (WU)	0.99	0.98–1.002	0.14

Sex and co-morbidity analyses were conducted as dichotomous variables

Body mass index, number and time to exacerbation, hospitalization duration, lung function tests, and parameters of right heart catheterization were analyzed as continuous variables

For continuous variables, HRs represent the change in mortality risk per 1-unit increase in the variable (e.g., per 1 year for age, per 1% predicted for lung function parameters, or per 1 mmHg for hemodynamic variables)

*Bold signifies *P*-value of ≤ 0.05

95%CI = 95% confidence interval, 6MWD = six-minute walk distance, CO = cardiac output, CI = cardiac index, COPD = chronic obstructive pulmonary disease, DLCO = diffusing lung capacity for carbon monoxide, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, HR = hazard ratio, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistant, RV = residual volume, TLC = total lung, WU = wood units capacity

0.01), and depression (HR 1.81, 95%CI 1.15–2.83, P = 0.009) were the variables most significantly associated with mortality.

SURVIVAL ANALYSIS

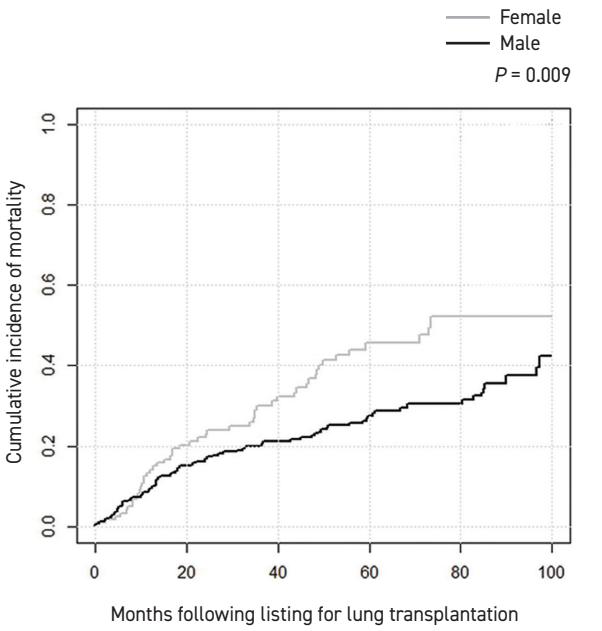
Figure 1 illustrates the cumulative incidence of mortality for lung transplant waitlist candidates stratified by sex using the Fine and Gray model. The cumulative incidence of mortality was consistently higher in females than in males during the post-listing follow-up period, demonstrating a significant difference between the groups (P = 0.009). The 1-year mortality rates were 40.3% in females versus 29.8% in males (P = 0.01).

Table 3. Multivariate analysis for prognostic factors for mortality in lung transplantation waitlist patients with COPD

Variable	HR	95%CI	*P*-value
Female sex	1.55	1.05–2.29	0.02
Age	1.02	1.002–1.054	0.03
Ischemic heart disease	1.69	1.12–2.48	0.01
Cerebral vascular accident	2.09	0.91–4.83	0.08
Depression	1.81	1.15–2.83	0.009

95%CI = 95% confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio

Figure 1. Cumulative incidence of mortality since listing for lung transplantation according to the Fine and Gray model



DISCUSSION

We conducted an analysis to evaluate sex differences in mortality risk among COPD patients awaiting lung transplantation. In Israel, there is a unique situation where the waiting time for lung transplantation is significantly longer compared to Western countries, such as the United States. This extended wait time has provided an opportunity to conduct prolonged follow-up on end-stage COPD patients and examine the mortality differences between the sexes.

Our main findings indicate that female sex significantly increases the risk of mortality on the waitlist. This finding corroborates that of Hull and colleagues [6], who identified female sex and prolonged waiting times as significant predictors of waitlist mortality during double lung transplantation. Notably, COPD patients, particularly females with chronic bronchitis, are at a greater risk for COPD-related deaths [7]. Silverman et al. suggested that this finding could be due to higher rates of COPD-related hospitalizations in females than in males [8], compounded by the known sex differences of the impact of smoking on lung function, which makes females more susceptible to its harmful effects [9,10]. While Silverman et al. suggested that higher rates of COPD-related hospitalizations could explain the increased risk of mortality, our study specifically examined exacerbation frequency and prolonged hospital stays as potential predictors. This finding is supported by our data, which showed that increased exacerbation rates were a significant risk factor for mortality. Although the association between higher exacerbation rates and female sex did not reach statistical significance, a trend toward increased exacerbation rates among female patients was observed. However, these factors demonstrated minimal impact compared to sex, age, and co-morbid conditions Therefore, a possible explanation for the observed sex differences mortality could be the presence of specific co-morbidities that are more prevalent in the female sex.

In our study, we found that depression, which was more prevalent in females than in males, significantly increased the risk of mortality on the waitlist. This association is supported by findings from Lisspers and co-authors [11] study, a large, real-world retrospective cohort analysis from Sweden, which reported a higher prevalence of co-morbidities such as asthma, depression, and anxiety among females. Moreover, Rahi et al. [12] noted that COPD patients with co-morbid anxiety or depression were more likely to present with acute exacerbations, rehospitalization, and increased mortality. These findings highlight the complexity of managing COPD in patients with significant psychological co-morbidities and underscore the importance of addressing these factors in the clinical care and allocation processes for lung transplantation.

Depression significantly affects COPD-related mortality through a combination of physiological and psychosocial mechanisms. It shares a genetic overlap with COPD, where inflammatory markers such as sTNFR-1 spill over into the bloodstream, potentially worsening lung function and increasing the frequency of exacerbation [13]. Psychosocially, depression lowers quality of life, increases disability, and reduces physical activity, which in turn heightens vulnerability to infections [14]. In addition, depression is a notable predictor of hospital readmissions due to deteriorating socioeconomic conditions and noncompliance with treatment plans, further increasing mortality risks [15]. These complex interactions underscore the necessity for integrated treatment approaches that simultaneously address COPD and mental health to enhance patient outcomes.

In our study, females were significantly more likely to have coexisting asthma compared to males. This finding is supported by Cosio et al. [16], who found that patients with coexisting asthma had twice the 1-year mortality rate compared to those with only COPD. Moreover, Lange and colleagues [17] reported that individuals with coexisting asthma, particularly those with late-onset asthma, were more prone to rapid lung function deterioration and have a higher risk of acute hospital admissions due to respiratory diseases compared to those with only COPD. This finding could also potentially explain the increased mortality observed in female patients. In our study, female patients demonstrated a poorer physiological status, reflected by lower 6MWD results and higher TLC values. These observations might be attributable to the coexistence of asthma in female patients.

Another possible cause for female increased risk of mortality could be due to the previously used LAS potentially discriminated against female patients by not adequately accounting for sex differences in its scoring system, leading to longer waiting times and fewer transplants for women compared to men. This viewpoint is supported by Beerman et al. [18], who noted that during the LAS era, male patients generally experienced de-

creased waitlist times and higher likelihood of receiving a transplant. Wille and co-authors [19] suggested that such disparities could be influenced by patient-specific factors that affect access to suitable donor organs, such as smaller physical stature in females. The replacement of LAS with the CAS as of 9 March 2023, aimed to mitigate these biases by not directly incorporating sex into its criteria [20]. Preliminary findings, including those from Valapour et al. [20], indicated that under the CAS, transplant rates for shorter candidates, especially those under 158 cm, have improved, thus reducing previous biases against female candidates. Both sexes have shown decreased mortality, but the impact has been more pronounced for females, suggesting a positive shift toward more equitable organ allocation in lung transplantation.

Given these findings, we recommend that female patients receive more frequent follow-up appointments. This advice is particularly important for early detection and management of co-morbidities such as depression and coexisting asthma, which may increase the risk of mortality. Regular monitoring of these conditions can help identify female patients who are at higher risk and ensure timely intervention to improve their outcomes.

Our findings indicate that female COPD patients on the lung transplant waitlist exhibit significant air trapping, as evidenced by higher RV and TLC compared to males. It is important to consider alternative or adjunctive treatment strategies for these patients. One such option is lung volume reduction procedures, including bronchoscopic lung volume reduction or lung volume reduction surgery, both of which have been shown to improve lung function, dyspnea, and quality of life in select COPD patients with severe hyperinflation. These procedures may serve as a supportive intervention for patients experiencing prolonged wait times for lung transplantation, particularly in healthcare systems like Israel's, where donor lung availability is limited. Future studies should explore the impact of lung volume reduction in female COPD patients with severe air trapping who are awaiting transplantation.

The current study has several strengths, including being one of the first to investigate a cohort of end-stage COPD patients who are on waiting list as candidates for lung transplantation, providing valuable insights into the prognostic significance of sex while accounting for critical variables such as the number of exacerbations and duration of hospital admission within the first year of entering the transplant waiting list and psychological co-morbidities. However, the study has limitations. Its retrospective, single-center design may limit the generalizability of the findings. In addition, the absence of a control group and the exclusive focus on COPD patients who are on waiting lists for lung transplantation. To further substantiate our findings, prospective studies with larger, more diverse populations are necessary.

CONCLUSIONS

In our cohort, female sex was independently associated with higher waitlist mortality, possibly reflecting a greater burden of co-morbidities (depression and coexisting asthma), lower total lung capacity, and reduced 6MWTD. Prospective, adequately powered studies are needed to validate this association and to determine whether sex-specific risk stratification or management strategies can improve outcomes.

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The wisest man is he who does not fancy that he is so at all.

Nicolas Boileau-Despreaux (1636–1711), often known simply as Boileau was a French poet and critic

Capsule

Mitochondrial ABHD11 inhibition drives sterol metabolism to modulate T-cell effector function

α/β-hydrolase domain-containing protein 11 (ABHD11) is a mitochondrial hydrolase that maintains the catalytic function of α-ketoglutarate dehydrogenase (α-KGDH), and its expression in CD4 + T-cells has been linked to remission status in rheumatoid arthritis (RA). **Jenkins** and colleagues showed that pharmacological inhibition of ABHD11 dampens cytokine production by human and mouse T-cells. Mechanistically, the anti-inflammatory effects of ABHD11 inhibition are attributed to increased 24,25-epoxycholesterol (24,25-EC) biosynthesis and subsequent liver X receptor (LXR) activation, which arise from a compromised tricarboxylic acid cycle. The impaired cytokine profile established by ABHD11 inhibition is extended to two patient cohorts of autoimmunity. Importantly, using murine models of accelerated type 1 diabetes, the authors showed that targeting ABHD11 suppresses cytokine production in antigen-specific T-cells and delays the onset of diabetes in vivo in female mice. Collectively, this work provides pre-clinical evidence that ABHD11 is an encouraging drug target in T-cell-mediated inflammation and may be a promising target for autoimmune disease treatment.

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Capsule

Fibroblasts remodeling the heart

Dilated cardiomyopathy is characterized by myocardial thinning, ventricular enlargement, and diminished cardiac function. It is a major cause of heart failure and is caused by a variety of mutations or acquired damage to the heart. Despite its prevalence, the pathogenesis of this disorder is not fully understood and treatments are limited. Given that fibrosis is a common feature of dilated cardiomyopathy and fibroblasts contribute to cardiac remodeling, **Bretherton** and co-authors examined the effects of a disease-causing mutation on fibroblasts. Although the mutation was only present in cardiomyocytes, it altered the functioning of surrounding fibroblasts, promoting their proliferation and extracellular matrix stiffening and thereby worsening cardiac function. Conversely, targeting mechanotransduction in these fibroblasts prevented the deleterious changes in cardiac structure and function.

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