APPENDIX

Lifetime Medical Costs Attributable to Sickle Cell Disease among Non-Elderly Individuals with Commercial Insurance

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Calculation of the KMSA estimator

Survival-adjusted SCD-attributable total and out-of-pocket costs were calculated using the following equation,

$$SCD\text{–}attributable\ costs_i = \sum S_i^{SCD} C_i^{SCD} - \sum S_i^{CO} C_i^{CO}$$

Where *S* is the probability of having survived to age *i* and C is the annual costs of survivors at age *i* for individuals with SCD (SCD) and matched controls (CO). The overall burden of SCD-attributable costs captured in Equation 1 encompasses both the intensity of excess costs incurred by surviving SCD individuals compared to matched controls and the cost-savings due to having higher mortality rates than matched controls[50]. An advantage of using the KMSA estimator is that it allows for decomposition of the total excess burden into its component intensity and mortality effects. Equation 1 can be rewritten as:

$$SCD\text{–}attributable\ costs_i = \sum S_i^{SCD}(C_i^{SCD} - C_i^{CO}) + \sum C_i^{CO}(S_i^{SCD} - S_i^{CO})$$

where the first part is the intensity effect, and the second part is the mortality effect. The variance of the KMSA estimator was obtained using the delta method, which determines the variance of the product of two conditionally independent stochastic quantities:

$$Var(S * C) = Var(S) * Var(C) + Var(S) * E(C)^2 + Var(C) * E(S)^2$$

We calculated $Var(C)$ using 1000 individual-level clustered bootstrapped replicates. To calculate $Var(S)$, we conducted binomial sampling with mean survival probabilities applied to 1,950 individuals (the starting cohort size in Lubeck et al.[27]). We calculated age-specific survival probabilities for males and females in 1000 bootstrap replicates.

Statistical Model of Costs for Survivors

We used a quasi-likelihood approach with generalized linear models and flexible link and variance functions to model total health care costs and OOP costs (in separate models)[24]. Goodness of fit was assessed using raw-scale residual-based analysis[25]. The regression results for total health care costs are shown below:

```
Extended GEE with Quadratic Variance Function    No of obs       =       90048
Optimization: Fisher's Scoring                   Residual df     =       90012
Variance:     (theta1*mu + theta2*mu^2)
Link:         (mu^lambda - 1)/lambda
Std Errors:   Robust
------------------------------------------------------------------------------
           y | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
y            |
       rind1 |  -.1584537   .0592894    -2.67   0.008    -.2746587   -.0422487
       rind2 |  -.0365767   .0589353    -0.62   0.535    -.1520877    .0789343
       rind3 |   .0446337   .0566887     0.79   0.431    -.0664741    .1557415
       rind4 |   .1656652   .0733571     2.26   0.024     .0218879    .3094426
    planind1 |  -.2464324   .0558485    -4.41   0.000    -.3558935   -.1369713
    planind2 |  -.1666441   .0687521    -2.42   0.015    -.3013957   -.0318926
    planind3 |  -.2183008   .0423459    -5.16   0.000    -.3012972   -.1353043
    planind4 |  -.1892055   .0452074    -4.19   0.000    -.2778104   -.1006005
    planind5 |  -.0222611   .0390545    -0.57   0.569    -.0988065    .0542843
    planind6 |  -.3680419   .0640599    -5.75   0.000     -.493597   -.2424869
    planind7 |  -.0733834   .0607798    -1.21   0.227    -.1925096    .0457429
    yearind1 |  -.3395468   .0452941    -7.50   0.000    -.4283217   -.2507719
    yearind2 |  -.2243535   .0433402    -5.18   0.000    -.3092987   -.1394084
    yearind3 |  -.1396276   .0423644    -3.30   0.001    -.2226603   -.0565949
    yearind4 |  -.1367749   .0541626    -2.53   0.012    -.2429316   -.0306182
    yearind5 |  -.0785478   .0420439    -1.87   0.062    -.1609523    .0038568
    yearind6 |  -.0840524   .0404675    -2.08   0.038    -.1633671   -.0047376
    yearind7 |  -.0464538   .0569081    -0.82   0.414    -.1579916     .065084
    yearind8 |   -.031775   .0460317    -0.69   0.490    -.1219955    .0584454
    yearind9 |   .0721245   .0525026     1.37   0.170    -.0307788    .1750277
   yearind10 |   .0475811   .0439127     1.08   0.279    -.0384862    .1336484
   yearind11 |   .0719153   .0435052     1.65   0.098    -.0133534    .1571841
     ageind1 |  -.0725437   .0486554    -1.49   0.136    -.1679066    .0228193
     ageind2 |   .2665828   .0556287     4.79   0.000     .1575527     .375613
     ageind3 |   .3792646   .0807021     4.70   0.000     .2210914    .5374378
     ageind4 |   .2114908   .1082412     1.95   0.051     -.000658    .4236397
     ageind5 |   .2180714   .1545759     1.41   0.158    -.0848918    .5210346
     ageind6 |   .4251936   .1873353     2.27   0.023     .0580232     .792364
    run_agec |   .0004878   .0039118     0.12   0.901    -.0071793    .0081549
   run_agec2 |   .0001211   .0001026     1.18   0.238      -.00008    .0003221
     female1 |  -.0836802   .0201018    -4.16   0.000     -.123079   -.0442813
     Nmonths |   .0925765   .0037198    24.89   0.000     .0852858    .0998673
       _cons |  -1.063492   .1315447    -8.08   0.000    -1.321315   -.8056687
-------------+----------------------------------------------------------------
lambda       |
       _cons |   .6367459    .041736    15.26   0.000     .5549448    .7185469
-------------+----------------------------------------------------------------
theta1       |
       _cons |   .3218515   1.541485     0.21   0.835    -2.699404    3.343107
-------------+----------------------------------------------------------------
theta2       |
       _cons |   9.886856   3.907951     2.53   0.011     2.227412     17.5463
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The regression results for OOP costs are shown below:

```
Extended GEE with Quadratic Variance Function    No of obs       =       90048
Optimization: Fisher's Scoring                   Residual df     =       90012
Variance:     (theta1*mu + theta2*mu^2)
Link:         (mu^lambda - 1)/lambda
Std Errors:   Robust
------------------------------------------------------------------------------
           y | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
y            |
       rind1 |  -.5305903   .0407225   -13.03   0.000     -.610405   -.4507756
       rind2 |  -.1782236   .0402637    -4.43   0.000     -.257139   -.0993082
       rind3 |   .0843788   .0398691     2.12   0.034     .0062367    .1625209
       rind4 |  -.3197721   .0472745    -6.76   0.000    -.4124284   -.2271158
    planind1 |  -.7704909   .0341067   -22.59   0.000    -.8373388    -.703643
    planind2 |  -.6758925   .0419552   -16.11   0.000    -.7581232   -.5936618
    planind3 |  -.9391512   .0292135   -32.15   0.000    -.9964086   -.8818939
    planind4 |  -.5870817   .0284457   -20.64   0.000    -.6428344   -.5313291
    planind5 |  -.2963437   .0263227   -11.26   0.000    -.3479353    -.244752
    planind6 |  -1.221872   .0485045   -25.19   0.000     -1.31694   -1.126805
    planind7 |  -.2453794    .028846    -8.51   0.000    -.3019164   -.1888423
    yearind1 |  -.3409517   .0312783   -10.90   0.000     -.402256   -.2796474
    yearind2 |   -.283074   .0347462    -8.15   0.000    -.3511753   -.2149726
    yearind3 |  -.2242791   .0273852    -8.19   0.000    -.2779531   -.1706052
    yearind4 |   -.163319   .0272298    -6.00   0.000    -.2166885   -.1099495
    yearind5 |  -.0805378   .0288702    -2.79   0.005    -.1371223   -.0239533
    yearind6 |  -.0784907   .0264543    -2.97   0.003    -.1303401   -.0266413
    yearind7 |  -.0521152   .0305403    -1.71   0.088    -.1119732    .0077427
    yearind8 |  -.0552346   .0291139    -1.90   0.058    -.1122967    .0018276
    yearind9 |   .1684591   .0365773     4.61   0.000     .096769    .2401492
   yearind10 |   .1310825   .0322429     4.07   0.000    .0678876    .1942774
   yearind11 |   .1585071   .0271914     5.83   0.000    .1052129    .2118014
     ageind1 |   .0156832   .0438837     0.36   0.721    -.0703274    .1016938
     ageind2 |   .1327992   .0321753     4.13   0.000    .0697368    .1958616
     ageind3 |   .2771352   .0481709     5.75   0.000    .1827219    .3715484
     ageind4 |   .3333095   .0674934     4.94   0.000    .2010249    .4655941
     ageind5 |   .2949299   .0895962     3.29   0.001    .1193246    .4705352
     ageind6 |   .3469824   .1049265     3.31   0.001    .1413301    .5526346
    run_agec |  -.0030738   .0022892    -1.34   0.179    -.0075605    .0014128
   run_agec2 |   .0001495   .0000599     2.50   0.013    .0000322    .0002668
     female1 |  -.0236897   .0136021    -1.74   0.082    -.0503494      .00297
     Nmonths |    .091246   .0028797    31.69   0.000    .0856018    .0968901
       _cons |  -.6839481   .0911074    -7.51   0.000    -.8625152   -.5053809
-------------+----------------------------------------------------------------
lambda       |
       _cons |   .4362815   .0411676    10.60   0.000    .3555945    .5169685
-------------+----------------------------------------------------------------
theta1       |
       _cons |   .8185535   .6356063     1.29   0.198     -.427212    2.064319
-------------+----------------------------------------------------------------
theta2       |
       _cons |   3.184539   1.615583     1.97   0.049    .0180536    6.351024
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Table 1: Raw total costs and out-pocket-costs for individuals with SCD. Costs are not model-estimated and shown as mean (standard error).

Age (years)	**Individuals with SCD**	
	Females	*Males*
	TOTAL MEDICAL COSTS	
0-5	$24,894 (1,388)	$32,098 (1,479)
6-12	$30,156 (1,386)	$31,404 (1,066)
13-18	$37,364 (1,295)	$43,676 (4,108)
19-24	$41,720 (1,435)	$43,054 (1,751)
25-34	$34,168 (767)	$36,529 (1,481)
35-54	$35,850 (698)	$39,808 (1,736)
55-64	$47,299 (1,529)	$46,320 (1,746)
	OUT-OF-POCKET COSTS	
0-5	$1,230 (93)	$1,305 (30)
6-12	$1,143 (25)	$1,216 (24)
13-18	$1,240 (28)	$1,280 (29)
19-24	$1,394 (30)	$1,354 (38)
25-34	$1,447 (38)	$1,327 (29)
35-54	$1,355 (18)	$1,326 (47)
55-64	$1,398 (24)	$1,393 (32)

Figure 1: Calibration and goodness-of-fit residual plots for annual total costs and OOP costs of surviving SCD individuals.

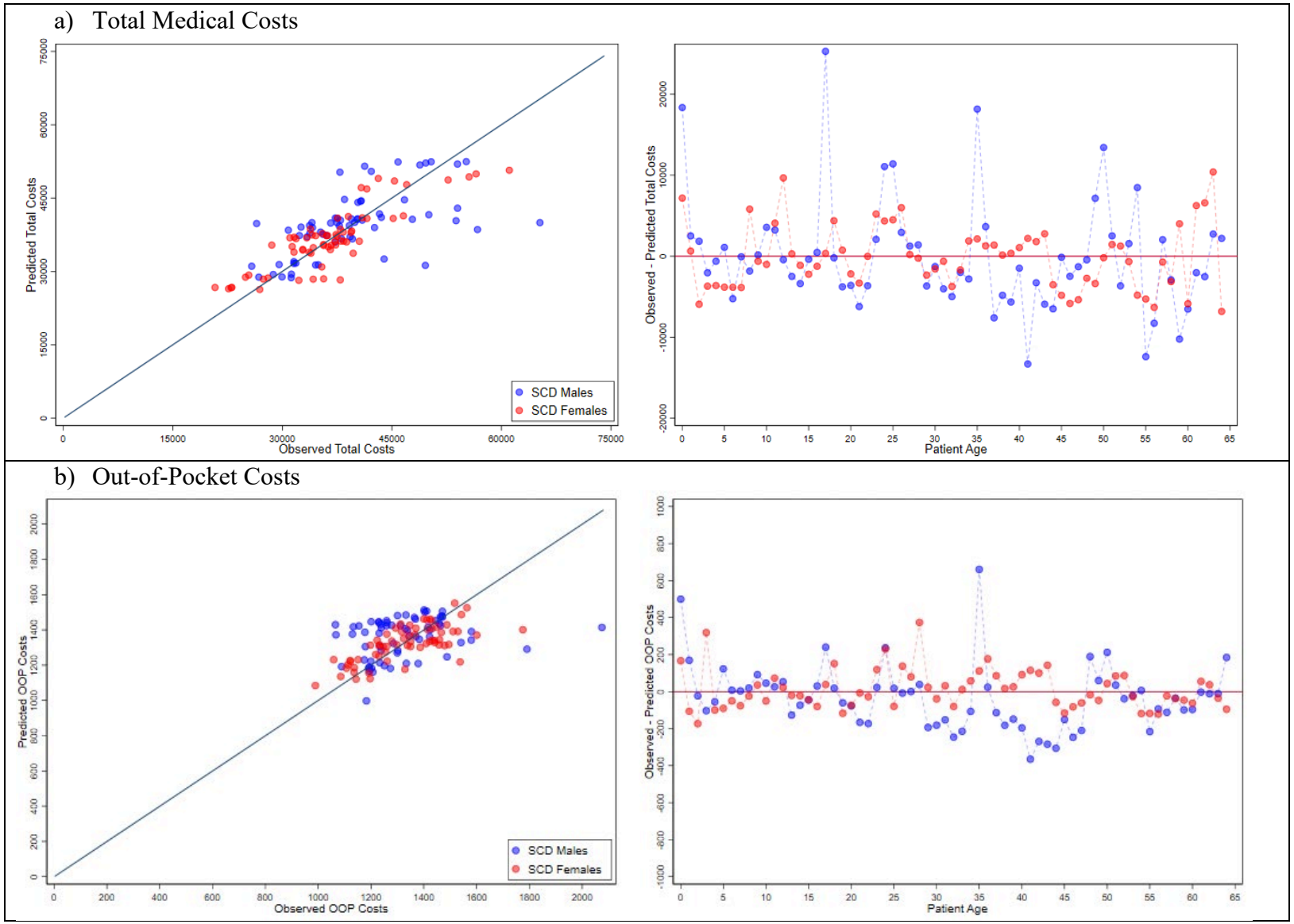

Figure 2: Estimated total costs and OOP costs among surviving SCD individuals smoothed over age. 95% confidence limits were estimated using 1000 individual-level clustered bootstrap replicates.

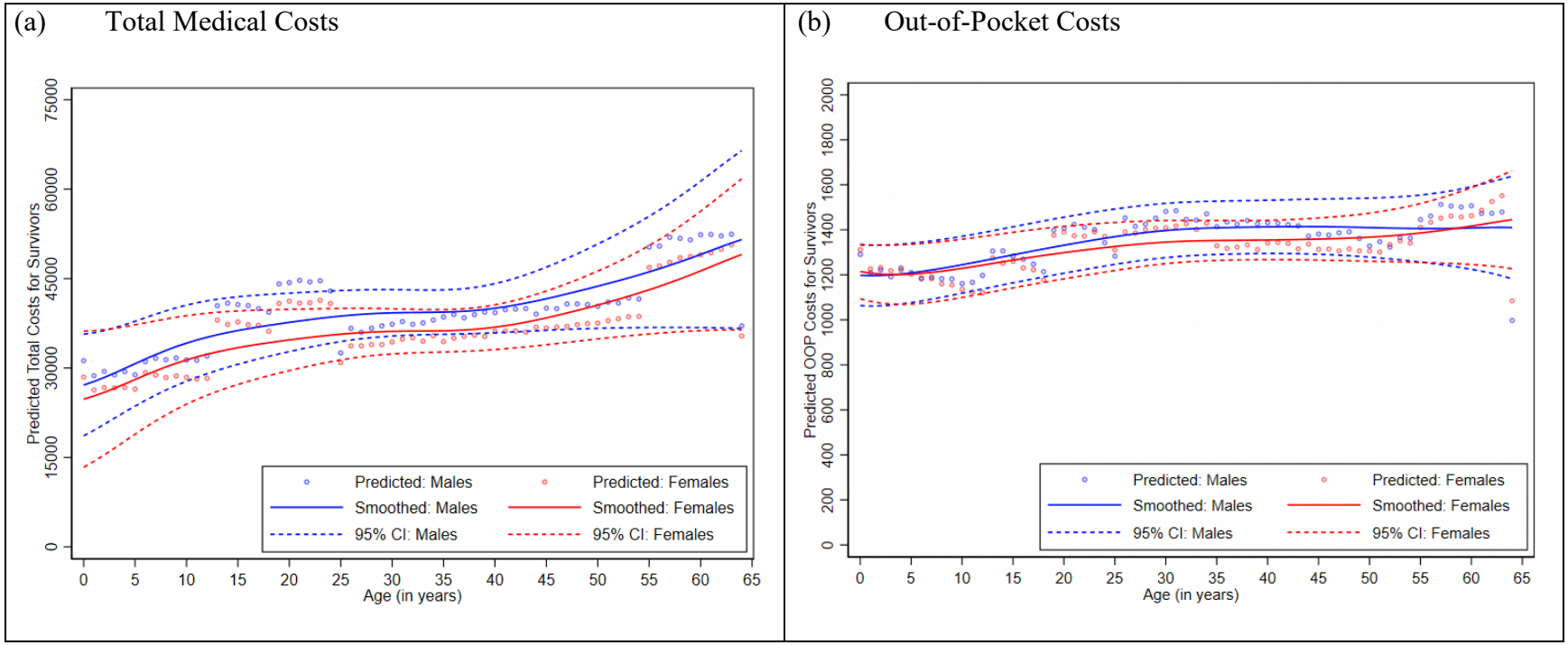

Figure 3: Digitized survival curves for SCD individuals and matched controls by sex.