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## Uptake and timing of bilateral prophylactic salpingo-oophorectomy among *BRCA1* and *BRCA2* mutation carriers

Angela R. Bradbury, MD<sup>#1,2</sup>, Comfort N. Ibe, BA<sup>#1,2</sup>, James J. Dignam, PhD<sup>3</sup>, Shelly A. Cummings, MS<sup>1,2</sup>, Marion Verp, MD<sup>1,4</sup>, Melody A. White, MS<sup>1,2</sup>, Grazia Artioli, MD<sup>5</sup>, Laura Dudliceck, MS<sup>1,2</sup>, and Olufunmilayo I. Olopade, MD<sup>1,2</sup>

<sup>1</sup>University of Chicago Center for Clinical Cancer Genetics, Chicago, Illinois

<sup>2</sup>Department of Medicine, Section of Hematology-Oncology, University of Chicago, Chicago, Illinois

<sup>3</sup>Department of Health Studies, University of Chicago, Chicago, Illinois

<sup>4</sup>Department of Obstetrics and Gynecology, University of Chicago, Chicago, Illinois

<sup>5</sup>Instituto Oncologico Veneto, Padove, Italy

# These authors contributed equally to this work.

### Abstract

**Purpose**—To evaluate prophylactic salpingo-oophorectomy uptake and timing among *BRCA1/2* mutation carriers in a cancer risk assessment program.

**Methods**—Clinical records of female *BRCA1/2* mutation carriers who received cancer genetic counseling between 1996 and 2003 were reviewed to determine the completion and the timing of prophylactic salpingo-oophorectomy. Logistic regression models evaluated associations between subject characteristics and surgery. Survival analysis methods were used to estimate the distribution of time to surgery.

**Results**—Among 88 women, 70% underwent prophylactic salpingo-oophorectomy. Prophylactic salpingo-oophorectomy was associated with older age, white race, having children, and a family history of ovarian cancer. Many women waited more than 12 months to undergo surgery and some delayed by several years. Younger age and not having children were associated with delays to surgery.

**Conclusion**—Prophylactic salpingo-oophorectomy is an acceptable risk reduction measure for many *BRCA1/2* mutation carriers. Some women make this decision many years after genetic testing. Continued discussion of the risks and benefits of risk reduction options may facilitate the uptake of recommended risk reduction interventions among *BRCA* mutation carriers.

## Keywords

*BRCA1; BRCA2; prophylactic salpingo-oophorectomy*

Women who carry a *BRCA1* or *BRCA2* mutation have a 31–87% risk of developing breast cancer and a 15–40% risk of developing ovarian cancer<sup>1–4</sup> compared with the risk in the general population of 12.5% and 1.5%, respectively.<sup>5</sup> In light of these risks, *BRCA* mutation carriers are counseled regarding available risk reduction methods, including prophylactic surgery, increased surveillance, and chemoprevention. One of these options, bilateral prophylactic salpingo-oophorectomy (BSO), has been shown to decrease the risk of ovarian cancer in *BRCA* mutation carriers by 85–96% and the risk of breast cancer by 50%.<sup>6–8</sup> In addition, surgical morbidity and mortality has decreased with the advent of laparoscopic surgical techniques.<sup>9</sup> Thus, BSO is currently recommended to *BRCA* mutation carriers between 35 and 40 years of age or at completion of childbearing.<sup>5,10</sup> Despite this, many women and clinicians are concerned about the effects of premature menopause after surgical prophylaxis.<sup>11,12</sup> Although there is some evidence suggesting that short-term hormone replacement therapy (HRT) does not increase breast cancer risks in *BRCA* mutation carriers, long-term prospective data are not available and many physicians are reluctant to provide, and many women are reluctant to consider postsurgical HRT.<sup>13</sup> Thus, some women elect not to undergo BSO and receive ovarian cancer surveillance with transvaginal ultrasound, serum CA-125, and clinical pelvic examination, although studies have suggested that the ability to detect early cancers with such screening is poor.<sup>14,15</sup>

Despite these recommendations and considering the controversy surrounding postsurgical HRT, the acceptability of BSO as a risk reduction method among *BRCA* mutation carriers has been questioned.<sup>16,17</sup> Reported rates of BSO among *BRCA* mutation carriers have varied from 13% to 75%.<sup>6,16–24</sup> Several studies have reported that the majority (50–75%) of mutation carriers undergo prophylactic salpingo-oophorectomy.<sup>6,18,19,21,23</sup> In contrast, other studies have reported lower rates (13–27%) of uptake of BSO among *BRCA* mutation carriers.<sup>16,17</sup> In these studies, surgical decision was assessed 12 months after genetic test results. Long-term decision-making regarding prophylactic salpingo-oophorectomy among mutation carriers has not been well described.

We hypothesized that some *BRCA* mutation carriers elect to undergo prophylactic salpingo-oophorectomy many years after test disclosure, based on age, concerns regarding premature menopause, and childbearing plans. If so, short-term assessments of BSO uptake may underestimate BSO rates and fail to accurately reflect the acceptability of this risk reduction measure among *BRCA* mutation carriers. In addition, delays in surgical decision-making could indicate a need for health care professionals to repeatedly discuss the risks and benefits of surgical prophylaxis over multiple clinical encounters. In this study, we evaluate salpingo-oophorectomy rates, time to BSO from test result disclosure, and factors associated with uptake of BSO among *BRCA* mutation carriers evaluated in a cancer risk assessment and prevention program.

## METHODS

### Study design and sample

We used a retrospective cohort design to evaluate the long-term uptake of BSO among *BRCA* mutation carriers who received clinical services at the University of Chicago Cancer Risk Clinic between January 1996 and December 2003. This study was approved by the Institutional Review Board at the University of Chicago.

Among all the 141 female *BRCA1* and *BRCA2* mutation carriers evaluated in the University of Chicago Cancer Risk Clinic between January 1996 and December 2003, those with a history of ovarian cancer ( $n = 17$ ), metastatic cancer at the time of evaluation ( $n = 4$ ), or a prior history of salpingo-oophorectomy for gynecologic reasons ( $n = 8$ ) were excluded. An additional 3 *BRCA* mutation carriers who elected not to obtain their genetic test results were excluded. Of 109 female mutation carriers (with at-risk ovarian tissue), 21 were excluded because of insufficient data or follow-up. The final cohort of 88 *BRCA* mutation carriers represents 81% of eligible women. There were no significant differences in ethnicity, mutation status (*BRCA1* versus *BRCA2*), or personal history of breast cancer between the 21 excluded *BRCA1/2* mutation carriers and those included in the analysis.

An extensive analysis of family and personal medical history was completed for all patients referred to the Cancer Risk Clinic to identify families suggestive of familial or hereditary cancer. Once identified, genetic counseling as well as recommendations for cancer risk reduction interventions are provided. Some participants, but not all, elect to have formal genetic testing. Risk reduction recommendations are conveyed in person during the initial genetic counseling session and after genetic testing and test disclosure. In addition, these recommendations are included in a patient letter that is sent after disclosure of genetic test results. Consistent with current guidelines,<sup>10</sup> BSO is routinely recommended to mutation carriers older than 35 years or at the completion of childbearing. Alternative ovarian risk reduction options routinely discussed include ovarian cancer screening (pelvic exam, transvaginal ultrasound, and CA-125) and oral contraceptive use. Prophylactic surgeries are recorded in the patient chart, and pathology reports are requested for all prophylactic surgeries.

Medical records were reviewed for all eligible female *BRCA1/2* mutation carriers with at-risk ovarian tissue. Age, mutation status, self-reported race, genetic test date, test disclosure date, personal history of breast cancer and/or mastectomy, number of children, number of first-degree and second-degree relatives with breast and ovarian cancer, completion of prophylactic salpingo-oophorectomy, date of BSO, and date of last follow-up were recorded.

### Statistical analysis

Logistic regression models were used to evaluate the association between each participant characteristic and surgery. In these models, robust variance estimates were used to account for possible clustering effects due to some participants in the study cohort being related.<sup>25</sup> These univariate analyses were followed by evaluation of multiple characteristics jointly as predictors of surgery, using all characteristics that showed association at  $P < 0.10$ . Results for associations are reported as odds ratios with confidence intervals.

For the analysis of surgery timing, censored data methods were used. The distribution of time to surgery or last follow-up was estimated using the Kaplan-Meier method.<sup>26</sup> To evaluate factors associated with time to surgery, the Cox proportional hazards model was used, incorporating variance adjustment for observations clustered by family relation.<sup>26</sup>

## RESULTS

### Sample characteristics and uptake of prophylactic bilateral salpingo-oophorectomy

Characteristics of the study sample are described in Table 1. The median age of women in the sample was 42 years (range, 23–71 years). Fifty-eight percent of women were older than 39 years, and 75% were older than 34 years when they received their genetic test results. Among 88 *BRCA* mutation carriers, 62 (70%) had undergone BSO. The median age at the time of surgery was 44 (range 30–68) years. Sixteen women elected to have BSO before undergoing genetic testing, accounting for 26% of the total sample who had a BSO.

### Predictors of prophylactic bilateral salpingo-oophorectomy

Several factors were associated with BSO in a univariate analysis that took into account clustering among related participants (Table 2). These included older age at genetic testing, having children, a personal history of breast cancer, non-Hispanic white race, history of mastectomy (treatment or prophylactic), and a family history of ovarian cancer. Participants with more than three relatives with a history of breast cancer were less likely to undergo BSO in the univariate analysis. In the multivariate analysis, older age, non-Hispanic white race, having children, and a family history of ovarian cancer remained statistically significant. Women with three or more relatives with breast cancer again were significantly less likely to have undergone BSO.

### Timing of prophylactic salpingo-oophorectomy

Among all the 46 mutation carriers who underwent BSO after receiving their genetic test results, the majority had their surgery within 15 months of their test result. Yet, many women waited more than 12 months to undergo surgery (from 17 to 112 months), and four women underwent BSO more than 3 years after receiving their genetic test results. The distribution of time to BSO was estimated, and factors related to timing of surgery were investigated (excluding those who underwent surgery before genetic testing [16 women]). Among these 72 women, the median follow-up from testing was 48 months (range <1–112 months). Median time to surgery was approximately 12.5 months (Fig. 1). Factors from Table 1 were examined for association with surgery timing. Among these, younger age at testing and not having children were most strongly associated with deferral of surgery (Fig. 2, A and B).

### Ovarian cancers

Among the 62 *BRCA* mutation carriers who underwent BSO, two epithelial ovarian cancers and one tumor of low malignant potential were detected on pathologic review of the surgical specimens. A papillary serous tumor of low malignant potential was identified in a 48-year-old woman. The other two ovarian cancers were high-grade papillary serous tumors in two women who were 35 and 61 years old at the time of surgery.

## DISCUSSION

In this study we found that the majority of *BRCA* mutation carriers elect to undergo BSO, although many make this decision over time and in some cases many years after receiving genetic test results. The high uptake of BSO among our population (70%) is consistent with several previous studies<sup>6,18,19,23,24,27</sup> and is higher than those reporting low rates of BSO uptake.<sup>16,17,28</sup> Differences in published rates of BSO use among mutation carriers may be related to several factors. The extended follow-up of many participants in our study, with women electing to undergo BSO several years after their genetic testing, could contribute to our higher rate of BSO use and underscores the need for long-term follow-up among mutation carriers. Studies evaluating short-term surgical decision-making may underestimate BSO use if women delay surgery, especially among cohorts with younger nulliparous women. In addition, differences among the populations studied could contribute to the variability in BSO rates. Women enrolled in research programs offering free genetic testing may differ significantly from those who present for clinical genetic testing, where testing is covered either by medical insurance or out-of-pocket payment. In addition, BSO rates may be higher in studies conducted after 2002, when the first prospective study suggested that prophylactic salpingo-oophorectomy also reduces breast cancer risk among *BRCA* mutation carriers,<sup>6–8</sup> potentially increasing the acceptability of BSO among *BRCA* mutation carriers or their health care providers. Thus, studies with short-term follow-up, assessments before 2002, and select populations may have underestimated the acceptability of BSO among *BRCA* mutation carriers. Our data suggest that BSO is an acceptable risk reduction measure for the majority of *BRCA* mutation carriers seeking evaluation and care in a clinical setting.

Our high rate of BSO, and specifically delayed BSO, may be related to the clinical services and structure of our cancer risk assessment program. Many women in our multidisciplinary clinic receive continued cancer screening and risk assessment, where health care providers readdress cancer risk assessment and risk reduction options at each semiannual or annual visit. For women who are candidates for BSO, this includes repeated discussions regarding the pros and cons of risk reducing prophylactic oophorectomy. In a study evaluating medical informational processing needs of *BRCA* mutation carriers considering prophylactic salpingo-oophorectomy, Babb et al.<sup>29</sup> found that many women expressed a need to consider the medical implications of BSO in the context of their individual experiences, perceptions, and psychosocial needs. Miller et al.<sup>30</sup> compared enhanced genetic counseling with standard genetic counseling and found that women in the intervention group were more likely to have sought out additional information about preventive options and to have undergone preventive surgery. Thus, the follow-up and counseling in our clinic may have contributed to the high rate of BSO use. Continued discussion of the medical and psychosocial impact of BSO may facilitate uptake of the procedure, and BSO uptake may be lower in settings where genetic services are limited to 1–2 visits with long-term follow-up relegated to the patient's oncologist or primary care physician.

In contrast to previous reports, we found that many *BRCA* mutation carriers delay prophylactic salpingo-oophorectomy, some for as many as several years after learning that they carry a *BRCA* alteration. Several studies have suggested that the majority of *BRCA*

mutation carriers make the decision to undergo BSO shortly after receiving their genetic test results.<sup>18,19,27</sup> In one study, 89% of *BRCA* mutation carriers underwent BSO within 9 months of learning their genetic test results and only 2 of 79 (<3%) waited more than 2 years.<sup>18,19</sup> Similarly, another study reported a median time to surgery of 4.6 months.<sup>27</sup> In contrast, many women in our cohort elected to have surgery more than 12 months after learning of their *BRCA* mutation, with a median time to surgery of 12.5 months, and some women waited several years to undergo surgery. Younger age and not having children were associated with delays to surgery. These data suggest that personal and childbearing factors may be important for *BRCA* mutation carriers considering prophylactic BSO and are consistent with a report by Ray et al.<sup>31</sup> suggesting that concerns about the timing of surgery were a primary factor for indecision about BSO among women at high risk for breast and ovarian cancer. Our data suggest that longitudinal studies may be necessary to adequately assess the true acceptability and optimal timing of prophylactic salpingo-oophorectomy in this high-risk population.

Despite an overall high rate of BSO in our study, there are clearly *BRCA* mutation carriers that elect not to have this recommended risk-reducing surgery. Women who were white, older, had children, and had a family history of ovarian cancer were more likely to have undergone BSO. As age and having children were also associated with a delay to surgery, these may not be significant barriers but indicators of the importance of life stage, timing, and concerns regarding premature menopause. On the other hand, nonwhite racial background and perceived cancer risk may be barriers to the uptake of BSO among *BRCA* mutation carriers. Consistent with previous studies,<sup>16,27</sup> *BRCA* mutation carriers with a family history of ovarian cancer were more likely to have undergone BSO than those with no experience of ovarian cancer in their family. These findings may reflect the impact of perception of risk on the decision to undergo BSO. Greater perception of ovarian cancer risk has been associated with utilization of BSO among *BRCA* mutation carriers.<sup>23,24</sup> Women without a history of ovarian cancer in their family may not think that they are at sufficiently high risk to undergo prophylactic surgery. Similarly, *BRCA* mutation carriers with a strong family experience of breast cancer may be most worried about their risk for breast cancer and perceive their risk of ovarian cancer as low. Further evaluation of how perceived cancer risk impacts risk reduction decision-making and how interventions to facilitate accurate understanding of cancer risk impact decision-making are needed.

Very few studies have evaluated risk-reducing health behaviors in *BRCA* mutation carriers among African American or other minority populations. Consistent with previous studies suggesting low uptake of genetic testing among minority populations,<sup>32</sup> we had a relatively small percentage of minority patients (11%). Regardless, this representation of minority *BRCA* mutation carriers is higher than most other studies evaluating BSO uptake in this population. In addition, although the number of nonwhite participants was small ( $n = 10$ ) and ethnic groups were combined, there was a significant difference in uptake of BSO among white versus nonwhite participants. Although these findings need to be confirmed in larger samples with evaluations of nonwhite ethnic groups independently, there is some literature supporting racial differences in health behaviors among women at high risk for breast cancer. In a study by Kinney et al.,<sup>33</sup> individuals from a single *BRCA1* African



American kindred reported a strong preference for surveillance rather than prophylactic surgery for cancer risk reduction. Similarly, Salant et al.<sup>34</sup> reported that African American women at high-risk for breast cancer are often skeptical of primary prevention options, including prophylactic surgery. Other studies have reported racial differences in mammography use and awareness and discussion of cancer risk and cancer prevention options among minority racial groups.<sup>35,36</sup> Thus, our findings are consistent with the body of literature suggesting the presence of racial differences in the acceptability of primary and secondary prevention of cancer, and specifically, prophylactic surgery. Although, these findings must be confirmed in prospective studies including larger numbers of minority *BRCA* mutation carriers, they underscore the need for further study of barriers and preferences for cancer prevention in minority populations at high risk for cancer.

The primary limitation of our study is the retrospective design and select population. In addition, some women may have undergone surgery, which was not recorded in their clinical record, although this would result in higher rates of BSO use. Although these findings were conducted in a clinical setting, the population still represents a highly motivated group presenting for specialized care and may be not be reflective of women presenting for genetic testing in the community. Although the racial differences noted are compelling, the number of nonwhite participants was small and future studies recruiting a higher number of minority *BRCA* mutation carriers are needed to confirm our findings.

In conclusion, these findings suggest that BSO is an acceptable risk reduction measure for the majority of *BRCA* mutation carriers. In some cases, women make this decision many years after obtaining their genetic test results. Continued discussion of the risks and benefits of risk reduction measures by health care providers may facilitate uptake of recommended risk reduction interventions among *BRCA* mutation carriers. In settings where genetic services are limited to 1–2 visits, continued discussion of the risks and benefits of prophylactic surgery may need to be addressed during future clinical encounters with other health care professionals. In addition, there is a need for continued study of cultural and psychosocial barriers to risk-reducing prophylactic surgery in women at high risk for breast and ovarian cancer.

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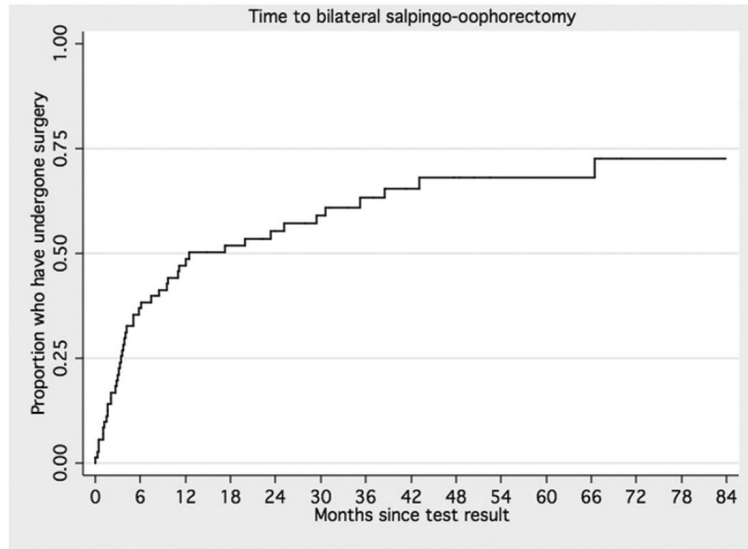
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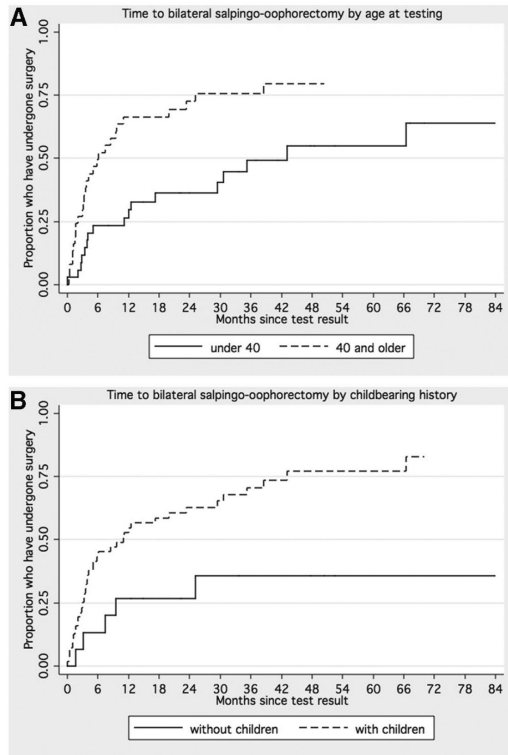
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**Fig. 1.**  
Time to bilateral salpingo-oophorectomy.



**Fig. 2.** Time to bilateral salpingo-oophorectomy (A) by age at testing and (B) by child bearing history.

**Table 1**Characteristics of *BRCA* mutation carriers eligible for prophylactic salpingo-oophorectomy ( $n = 88$ )

	<i>N</i> (%)
Age at testing, median (range)	42 (23–71)
Under 40 years	37 (42)
40 or older	51 (58)
Mutation status	
<i>BRCA1</i>	62 (70)
<i>BRCA2</i>	26 (30)
Ethnicity	
White	78 (89)
Black	8 (9)
Hispanic	2 (2)
Personal history of breast cancer	
Yes	52 (59)
No	36 (41)
History of mastectomy	
No mastectomy	42 (48)
Treatment mastectomy <sup>a</sup>	26 (30)
Prophylactic mastectomy <sup>a</sup>	31 (35)
No. children	
None	17 (19)
One child	14 (16)
2–3 children	50 (57)
4 or more children	7 (8)
No. FDRs and SDRs with breast cancer	
None	5 (6)
1–2	44 (50)
3–4	26 (30)
5 or more	13 (15)
No. FDRs and SDRs with ovarian cancer	
None	35 (40)
1	23 (26)
2	20 (23)
3 or more	10 (11)

FDR, first degree relative; SDR, second degree relative.

<sup>a</sup>Women could have had both a treatment and prophylactic mastectomy.

**Table 2**Associations with bilateral prophylactic salpingo-oophorectomy ( $n = 88$ )

	Had BSO, <i>N</i> (%)	No BSO, <i>N</i> (%)	Univariate test of association <sup>a</sup>			Multivariate test of association <sup>b</sup>		
			Odds ratio	Confidence interval	<i>P</i>	Odds ratio	Confidence interval	<i>P</i>
Age <40 yr	19 (51)	18 (49)	1.00	—		1.00	—	
Age 40 yr	43 (84)	8 (16)	5.09	1.82–14.24	0.002	12.77	2.22–73.50	0.004
Unaffected	20 (56)	16 (44)	1.00	—		1.00	—	
Had breast cancer	42 (81)	10 (19)	3.36	1.33–8.51	0.011	2.13	0.49–9.16	0.311
<i>BRCA1</i>	44 (71)	18 (29)	1.00	—				
<i>BRCA2</i>	18 (69)	8 (31)	0.92	0.36–2.435	0.862	—		
Non-White	4 (40)	6 (60)	1.00	—		1.00	—	
White	58 (74)	20 (26)	4.35	1.15–16.40	0.023	13.80	3.02–63.04	<0.001
No mastectomy	25 (60)	17 (40)	1.00	—		1.00	—	
Mastectomy	35 (80)	9 (20)	2.45	0.91–6.61	0.077	1.48	0.30–7.26	0.632
No children	8 (47)	9 (53)	1.00	—		1.00	—	
Have children	54 (76)	17 (24)	3.57	1.19–10.74	0.023	7.47	1.32–42.24	0.023
Family history of ovarian cancer								
No	18 (51)	17 (49)	1.00	—		1.00	—	
Yes	44 (83)	9 (17)	4.62	1.63–13.12	0.004	6.46	1.11–37.63	0.038
No. relatives with breast cancer								
0	22 (81)	5 (19)	1.00	—	0.009	1.00	—	0.016
1–2	32 (80)	10 (20)	0.91	0.24–3.45		2.65	0.63–11.16	
3 or more	8 (38)	13 (62)	0.14	0.03–0.74		0.22	0.03–1.85	

<sup>a</sup>Chi-squared tests to assess associations between prophylactic oophorectomy and sample characteristics were computed accounting for clustering by family unit via robust variance estimates.

<sup>b</sup>From a model including all variables shown.