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A Method to Estimate Off-Schedule Observations in a Longitudinal Study

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Abstract

Purpose—Data in epidemiological studies sometimes are collected off-schedule from planned study visits. In an ancillary study to the Study of Women's Health Across the Nation (SWAN), longitudinal breast density data were collected retrospectively from mammograms that were not acquired at the study visits. We propose a method to estimate the off-schedule breast density measurements at the time of study visits.

Methods—This method uses local linear interpolation, with multiply imputed error terms drawn from assumed subject-specific normal distributions based on the within-subject standard deviations of mammographic density measurements. We evaluate the validity and implications of this approach.

Results—Coefficients of random intercept models assessing the association between annual changes in body mass index and dense breast area estimated with this approach ($\beta = -0.17$, $P = 0.46$) differed from those obtained when each mammogram was matched to the nearest study visit ($\beta = -0.30$, $P = 0.04$). The proposed estimation approach had a small average prediction error (0.11 cm²).

Conclusions—Because matching does not incorporate breast density changes over time, our local linear interpolation with multiple imputation approach may provide more accurate results. The

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proposed approach is applicable to other epidemiologic studies with off-schedule data where the missing variable changes linearly over relatively short periods of time.

Keywords

Epidemiologic Methods; Missing Data; Multiple Imputation; Linear Interpolation; Mammography

Introduction

In epidemiologic research, data may be collected at times other than those planned in the initial study design, such as data from existing records. Such retrospectively collected data are unlikely to coincide with the study visits and can be considered off-schedule.

Off-schedule data were obtained in an ancillary study to the Study of Women's Health Across the Nation (SWAN) prospective cohort study(1),the SWAN Mammographic Density Substudy(2), where measures of breast density were obtained from retrospectively collected routine screening mammograms from a subset of SWAN participants. Although these mammograms were taken during the women's active participation in SWAN, their timing rarely coincided with the SWAN study visits (0.27%), when predictors such as body mass index (BMI) were collected. This created a missing data problem in our longitudinal analysis of mammographic density as a function of BMI(3). Matching each mammogram to the nearest SWAN visit was problematic, due to the high degree of both between- and within-subject variability in the relative timing of the mammograms and study visits. A matching algorithm would not account for either the time periods between study visits and mammograms or changes in breast density occurring over those periods.

To our knowledge, methods other than simple matching for estimating retrospectively collected supplementary data at study visit times have not been reported. We describe an approach to estimate off-schedule data at the time of study visits. We combine local linear interpolation (LLI), to estimate breast density measurements at the SWAN visits, based on adjacent off-schedule mammogram data) with a variant of multiple imputation to allow for uncertainty in the estimation.

Materials and Methods

Study population

The SWAN Mammographic Density Substudy has been described previously (2,4). Participants provided written informed consent, and institutional review board approvals were obtained for both SWAN and the SWAN Mammographic Density Substudy. We utilize the same population as in our previous analysis of anthropometry and breast density (3).

Description of data

Mammogram collection and density measurements in the SWAN Mammographic Density Substudy have been described (2,4). Briefly, three SWAN sites were purposefully-selected to include participants who were Caucasian, African American, Chinese, and Japanese. Starting after SWAN visit 6, investigators at these sites enrolled participants and obtained routine screening mammograms taken two years prior to the baseline SWAN visit through two years after SWAN visit 6. Participants and non-participants at these sites were similar in age (mean [SD] 45.9 [2.7] versus 45.6 [2.7], respectively, $p=0.06$), but non-participants were slightly heavier than participants (mean [SD] 71.0 kg [19.3] versus 66.8 kg [17.4], respectively, $p=0.0001$). Participants were also less likely to be African American (9.0%

versus 17.3%, $p < 0.0001$) and more likely to be premenopausal at baseline (58.4% versus 50.9%, $p = 0.01$). The timing and frequency of mammograms were not under experimental control. From 2 to 10 mammograms were collected on the 834 participants in the present analysis, with a median of 4. Breast density measurements were performed by a single reader using manual planimetry. We focus on the dense breast area to illustrate the proposed estimation approach.

Figure 1 shows a timeline of SWAN visits and mammograms for a prototypical participant (Participant X). Noteworthy features of Participant X's data include the lack of mammograms near some SWAN visits and the variable timing of mammograms in relation to the nearest SWAN visit.

Approaches for estimating dense breast area

Using the observed mammogram data, we assessed whether the change in dense breast area was linear over the observed study period. We fit a random intercept linear regression model with orthogonal polynomials for age, which demonstrated that higher order polynomials in age were necessary (data not shown). Thus we could not assume global linearity for the trajectory of the dense breast area. Linearity over shorter time periods appears to hold in this study; thus we chose to use linear interpolation as the basis for our estimation procedure.

We considered five approaches for estimating breast density at the visit times: 1) an algorithm matching each mammogram to the nearest visit, 2) LLI, 3) LLI with a singly imputed noise term, 4) LLI with multiply imputed noise terms, and 5) LLI with multiply imputed noise terms for visits >90 days from nearest mammogram and matching otherwise. Approach 5 is consistent with the belief that breast density is unlikely to undergo substantial changes within three months. Each approach has limitations related to incorporation of breast density changes, variance estimation, and the choice of noise terms, which are described in the Discussion section.

For Approaches 1 and 5, the matching occurred without regard to whether the mammogram preceded or followed the study visit or time interval between the two events. Approximately half of all mammograms matched to SWAN visits 1-6 were taken within 90 days of the respective visit (Visit 1, 45.2%; Visit 2 50.4%; Visit 3, 48.0%; Visit 4, 50.1%; Visit 5, 50.9%; Visit 6, 52.5%), though this was less frequent for visits 0 (28.4%) and 7 (36.9%). Kernel density estimates of the distribution of time between each SWAN visit and the matched mammogram are shown in Figure 2.

To implement the LLI, mammograms and SWAN visits were ordered chronologically. Data from the mammograms before and after a target SWAN visit were used to estimate breast density at that SWAN visit according to the following interpolation equation:

$$D_{i,t_j} = D_{i,t_{j-}} + s(D_{i,t_{j+}} - D_{i,t_{j-}}) \quad \text{Equation 1}$$

where

$$s = \frac{A_{i,t_j} - A_{i,t_{j-}}}{A_{i,t_{j+}} - A_{i,t_{j-}}} \quad \text{Equation 2}$$

and D is the dense breast area, i is an indicator for each participant “ i ”, t denotes time with t_j representing the time of the missing data (i.e., time of target SWAN visit) and t_{j-} and t_{j+} representing the times of the mammograms immediately before and after t_j , respectively. A scaling factor (s) for the time between the target SWAN visit and the nearest mammograms was computed using age (A) at the time of these events, measured in years to the first decimal place (using a similar notation as for D). This method assumes that breast density change is linear between the two consecutive mammograms but not necessarily linear overall. Because we did not extrapolate beyond the available data, visits without a mammogram both before and after the target SWAN visit were excluded. The LLI was implemented using the “`ipolate`” command in Stata version 10.0 (Stata Corporation, College Station, TX).

In Approaches 3-5 we added noise to each interpolated value to account for the error introduced by interpolating breast density rather than measuring it at the SWAN visit. For each participant we estimated the standard deviation (SD_i) of her observed dense breast area measurements. Person-specific normal distributions of noise terms were generated, with a mean of 0 and SD_i equal to the estimated SD of the participant's observed dense breast areas. A common SD was not indicated due to substantial variability in the within-subject SD for dense breast area (average 6.34, range 0 – 45.79). In Approach 3, a randomly selected noise term from this distribution was added to each interpolated value. For Approaches 4 and 5, multiple imputation was used to create ten analytic datasets, each with a random noise term added to the linearly interpolated value of dense breast area. Up to 10 imputations may be needed in situations with high levels of missing data (5,6). Due to the addition of the random noise terms, some implausible negative values for dense breast area were obtained (<1%). These implausible values were discarded and new random noise terms were generated. Figure 3 displays the observed and estimated mammogram data for Participant X, using Approach 5.

In a sensitivity analysis, we considered a locally averaged estimator of the within-subject SD, based on the average variance of adjacent pairs of mammograms. Dense breast area was estimated under each Approach using these alternative noise terms.

Illustrative example

We modeled the longitudinal relationship between annual changes in BMI and annual changes in dense breast area under each Approach. Annual changes were calculated by standardizing the change in each variable between each participant's consecutive visits to a one year time period. Random intercept regression models were fit using the “`xtreg`” command in Stata version 10.0 using the participant's age in days as the time scale. The random intercept model was chosen to allow for the substantial between-subject heterogeneity observed in this study.

Regression models were fit using breast density estimates from each Approach using a common set of 803 subjects for whom density measurements were estimable using all five approaches. For Approaches 4 and 5, each set of ten regression coefficients and their variances was combined to obtain an overall multiple imputation estimate of the regression coefficient and its variance using Rubin's rules (5,7). Multiple imputation estimates of the regression coefficients and their variances were calculated using the “`mjoin`” and “`micombine`” commands in Stata. We compared the magnitudes of the regression coefficients and their variances across the five approaches considered. All statistical tests performed were two-sided, with $P \leq 0.05$ considered to be statistically significant.

Design of validation study

Using the observed mammographic density data among participants with at least three mammograms, data for one mammogram between the first and last mammogram were randomly set to missing. Approaches 1-4 were used to estimate the density measurements for the “missing” mammogram data. For descriptive purposes, in Approach 4 a single estimated value was calculated as the average of the ten imputed values. Approach 5 was not considered because no participants had mammograms separated by <90 days. Prediction error was estimated by subtracting the observed value from the fitted value for each approach. We compared the prediction errors from Approaches 1-4. We considered estimates to be “poor” when the prediction error was greater than 10 cm² and the estimated value differed from the observed by more than 10%. We used analysis of variance (ANOVA) to compare the magnitudes of the prediction errors by the reported quality of the mammograms (poor, fair, good, or excellent). We used Pearson correlation coefficients to quantify associations between the estimates from Approaches 1-4 with each other and with the observed values. We also calculated a Pearson correlation coefficient to quantify the association between average annual change in dense breast area estimated from the observed data and estimated from the linearly interpolated data.

Results

Table 1 describes the study population at SWAN enrollment. A complete description of the study population has been reported previously(3). The mean dense breast area from participants' first available mammogram was 46.2 cm² (SD 26.7). Subjects included in this analysis were followed for an average of 4.8 years (SD 1.8). On average, dense breast area changed by -0.77 cm² (between-subject SD 4.49) annually.

SWAN example

Table 2 summarizes the random intercept regression models. The association between annual change in BMI and annual change in dense breast area was strongest and statistically significant under the matching algorithm (Approach 1: $\beta = -0.297$, $P = 0.04$). LLI and single and multiple imputation provided similar estimated regression coefficients (Approach 2: $\beta = -0.120$, Approach 3: $\beta = -0.109$, Approach 4: $\beta = -0.128$). Combining multiple imputation and close matching resulted in a slightly more extreme estimate (Approach 5: $\beta = -0.169$). Estimated variance was lowest for Approach 2 (variance=0.004) and was increased for Approach 1 (variance=0.021) and Approach 3 (variance=0.023). Variance was highest using Approaches 4 (variance=0.049) and 5 (variance 0.049). Neither the regression coefficients nor their variances were appreciably changed for any Approach when the alternative noise terms (i. e. derived from locally averaged SD_i) were used (data not shown).

Validation study

The validation study included 710 participants with ≥ 3 mammograms. Although the mean prediction error was similar across approaches, Approaches 1 and 3 showed the greatest variability (data not shown). For Approach 4, the mean prediction error was 0.11 cm² and approximately 50% of the estimates were within 4 cm² of the observed measurement.

Estimates from each approach were highly correlated with the observed dense breast area and with each other ($r \geq 0.93$, data not shown). The average annual dense breast area change estimated from the observed data and estimated from the LLI data (Approach 2) were moderately correlated ($r = 0.52$, $p < 0.001$); the correlation was improved ($r = 0.70$, $p < 0.001$) when a single outlier was excluded.

Figure 4 shows examples where Approach 4 did (Participant Y) and did not (Participant Z) work well. For Participant Y, the change in density across mammograms 4, 5, and 6 was approximately linear, and the multiple imputation estimate of dense breast area (32.2 cm²) was very close to the observed value (32.8 cm²). Our method provided poor estimates when breast density underwent a non-linear change across the estimation interval. Estimates were poor for 14.8% (N=105) of the participants. For Participant Z, the estimated dense breast area for mammogram 5 was 67.4 cm² while the observed dense breast area was 122.8 cm² (prediction error=-55.4 cm²). Interestingly, the film quality for this mammogram was poor, while the quality was higher for her other mammograms.

The majority of the mammogram films were rated as excellent (N=492, 69.3%) or good (N=178, 25.1%) quality, and fewer were fair (N=31, 4.4%) or poor (N=9, 1.3%). Film quality was more likely to be fair or poor in instances where the method worked poorly (10.5%), compared to instances where the method worked well (4.8% fair or poor, $P=0.02$). The prediction error from Approach 4 differed by film quality with the mean prediction error for poor (-3.60 cm²) or fair (3.14 cm²) quality films being larger than that for films of good (0.22 cm²) or excellent (-0.06 cm²) quality, though this association was of borderline significance ($P=0.10$ based on an ANOVA model).

Discussion

We have presented a procedure for estimating off-schedule outcome data at the times of scheduled study visits, using local linear interpolation followed by multiply imputed error terms to include uncertainty related to the variation of the original data measures. Because mammographic density is not expected to vary substantially over short periods of time, LLI was expected to work well. We also demonstrated how variations on our proposed method affect the results of regression analyses based on the observed SWAN mammogram data. In a validation study our estimated measurements were, on average, very close to the observed data. Problems arose when the mammogram data exhibited a non-linear trend over the estimation interval or the mammograms were of poor quality.

Multiple imputation is a valid method for obtaining unbiased estimates and appropriate variances for missing data(6,8-12). Our approach differs from standard ("proper") imputation in that our point estimates were not derived from the imputation process, i. e. our point estimates and error terms were derived separately. Although not optimal theoretically, this was done for practical reasons. We wanted to account for global non-linearity using a simple algorithm by constructing flexible, locally linear point estimates.

Though this paper is not intended to draw etiologic inferences, it is important to note how conclusions might change based on the estimation approach used. Based on the matching algorithm we would infer that change in BMI was significantly associated with change in dense breast area, while we would judge this association to be attenuated and non-significant based on other approaches.

The multiply imputed noise terms were randomly generated from distributions reflecting the variability of each participant's observed mammographic density data. The standard deviations used as the basis for the noise terms assume no trend in the mammogram data and are not well-estimated for women with relatively few measurements. We acknowledge that the assumed distribution of noise terms could greatly influence the results, though similar results were obtained when we repeated analyses using a locally averaged SD_i to generate the noise terms. Therefore, we present data incorporating our original noise terms to maintain consistency with our previously published results(3). Although other methods of choosing

noise terms are possible, the relatively small number of mammograms for many participants limited our ability to consider more complicated variance estimators.

We recommend using LLI with multiple imputation of error terms (Approach 4) in settings where the change is non-linear overall, but local linearity is reasonable. In cases that exhibit short-term stability, additionally preserving closely aligned data within an appropriate time interval (Approach 5) appears to perform well. These proposed methods to account for off-schedule observations have several advantages. Both provide ways for investigators to combine data outside of planned study visits with data collected at those visits, which increases the opportunities to utilize off-schedule data. The multiply imputed noise terms allow for uncertainty in the variance estimation while matching or single imputation do not. These approaches can be implemented easily using standard software.

The proposed method does have limitations. Some study visits were excluded because participants lacked mammograms either before or after a visit and we did not extrapolate density measurements outside the time frame of the observed data. Excluding such observations could result in decreased power and raises the possibility of a selection bias. Second, our tests of statistical significance could be overly conservative if the error distribution is misspecified. Third, this method does not account for measurement error either from the original density readings. Fourth, our choice of maintaining matches for mammograms taken within 90 days for Approach 5 is somewhat arbitrary. Data on short-term changes in breast density are not available, but we believe it is unlikely that breast density would change substantially within 90 days among women not initiating or ceasing use of hormone therapy during that time. An additional limitation is that the timing and frequency of mammograms in relation to the SWAN visits may not be non-informative, as we have assumed.

Finally, our method performs poorly when there is a substantial non-linear trend in the measurements over the estimation interval. Our validation study estimated the missing data using observations that typically were separated from each other by approximately two years. In reality, both mammograms and study visits occurred at approximately one-year intervals, with most participants having less than six months between a mammogram and the nearest study visit. Thus, the time period spanned by the interpolation in the SWAN example was typically shorter than that in the validation study, and the level of error in the application of the method to the real data is likely to be less than that observed in our validation study.

Ideally, studies would be designed such that all needed data were collected at coincident timepoints. In reality, issues with off-schedule data are likely to occur in other longitudinal studies. The proposed methods could be applicable to a wide variety of situations, such as estimating body weight at the time of a phone interview based on measurements recorded at preceding and subsequent clinic visits. Further development and evaluation of the proposed approach may be necessary before adoption elsewhere. Our SWAN example demonstrates that failure to account for the fact that observations are off-schedule can lead to questionable conclusions about the magnitude and significance of observed associations.

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List of Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index

LLI	Local linear interpolation
SD	Standard deviation
SWAN	Study of Women's Health Across the Nation

Figure 1.
Observed data from SWAN visits and retrieved mammograms for a prototypical participant.^{a,b}

Figure 2.
Kernel density estimates of the time between mammograms and nearest SWAN visit, by SWAN visit

Figure 3. Observed and estimated dense area measurements using Approach 5 for a prototypical participant.

Figure 4.

Examples of cases in the validation study where the linear interpolation with multiple imputation (Approach 4) performed well (Participant Y, (A)) and where the method resulted in a large prediction error (Participant Z, (B)).

Table 1
Characteristics of Study Population at SWAN Enrollment, Los Angeles, CA, Oakland, CA, and Pittsburgh, PA, 1996-2004

Characteristic	Total study population N=834
Age, years; mean (SD)	46.5 (2.7)
Race/site; N (%)	
African American/Pittsburgh	62 (7.4)
Caucasian/All Sites	407 (48.8)
Chinese/Oakland	182 (21.8)
Japanese/Los Angeles	183 (21.9)
Menopausal status; N (%)	
Premenopausal	483 (58.3)
Early perimenopausal	346 (41.7)
Body mass index; N (%)	
Underweight: <18.5 kg/m ²	16 (1.9)
Normal: 18.5 – <25 kg/m ²	478 (57.5)
Overweight: 25 – <30 kg/m ²	203 (24.4)
Obese: ≥30 kg/m ²	135 (16.2)
Mammograms; median (range)	4 (2 – 10)

SD, standard deviation

Table 2
Parameter Estimates for the Age-Adjusted Regression of Annual Change in Dense Area on Annual Change in Body Mass Index by Estimation Approach, N=803, Los Angeles, CA, Oakland, CA, and Pittsburgh, PA, 1996-2004

Approach to Estimating Dense Breast Area	N	β^a	Variance	P value
1) Simple matching of mammograms to visits	803	-0.297	0.0205	0.04
2) Local linear interpolation (LLI)	803	-0.120	0.0040	0.06
3) LLI with single imputation of noise terms	803	-0.109	0.0228	0.47
4) LLI with multiple imputation of noise terms	803	-0.128	0.0488	0.57
5) LLI with multiple imputation for observations with >90 days between mammogram and visit and matching otherwise	803	-0.169	0.0493	0.46

LLI, local linear interpolation

^aRegression coefficients have units of $\text{cm}^2/(\text{kg}/\text{m}^2)$