Research Article

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Kernel Density Estimation as a Measure of Environmental Exposure Related to Insulin Resistance in Breast Cancer Survivors

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Abstract

Background: Environmental factors may influence breast cancer; however, most studies have measured environmental exposure in neighborhoods around home residences (static exposure). We hypothesize that tracking environmental exposures over time and space (dynamic exposure) is key to assessing total exposure. This study compares breast cancer survivors' exposure to walkable and recreation-promoting environments using dynamic Global Positioning System (GPS) and static home-based measures of exposure in relation to insulin resistance.

Methods: GPS data from 249 breast cancer survivors living in San Diego County were collected for one week along with fasting blood draw. Exposure to recreation spaces and walkability was measured for each woman's home address within an 800 m buffer (static), and using a kernel density weight of GPS tracks (dynamic). Participants' exposure estimates were related to insulin resistance (using the homeostatic model assessment of insulin resistance, HOMA-IR) controlled by age and body mass index (BMI) in linear regression models.

Results: The dynamic measurement method resulted in greater variability in built environment exposure values than did the static method. Regression results showed no association between HOMA-IR and home-based, static measures of walkability and recreation area exposure. GPS-based dynamic measures of both walkability and recreation area were significantly associated with lower HOMA-IR ($P < 0.05$).

Conclusions: Dynamic exposure measurements may provide important evidence for community- and individual-level interventions that can address cancer risk inequities arising from environments wherein breast cancer survivors live and engage.

Impact: This is the first study to compare associations of dynamic versus static built environment exposure measures with insulin outcomes in breast cancer survivors. *Cancer Epidemiol Biomarkers Prev; 26(7); 1078–84. ©2017 AACR.*

Introduction

Breast cancer is one of the most common forms of cancer among women and a leading cause of cancer death with an estimated 40,290 deaths in 2015 (1). More than 70% of U.S. women ages 40 to 59 years are classified as overweight or obese (2). Furthermore, type II diabetes prevalence has increased by over 30% in the past 30 years (3). Diabetes and obesity are linked through complex pathways to breast cancer (4, 5). For example, obesity and type II diabetes-related insulin resistance are associated with chronic hyperinsulinemia, systemic and tissue-localized inflammation, oxidative stress, and increased extra-glandular estrogen production, which are thought to increase cancer risk (6, 7). A healthy diet and physical activity are key modifiable behavioral factors that can reduce breast cancer risk, cancer recurrence risk, and improve treatment effects by targeting biological mechanisms such as insulin resistance and inflammation (8–11). Understanding factors that support engagement in healthy lifestyle behaviors, and their relationship to cancer, is critical to understanding disparities in cancer and designing more effective interventions for women at risk for breast cancer.

Increasingly, health behavioral scientists are drawing on the Ecological Model of Behavior Change, which posits that individual health behaviors and outcomes exist within multiple levels of influence (individual, family, community, and policy). Therefore efforts to reduce breast cancer risk by promoting behavior change must consider more than the individual (12, 13). Under this model, greater attention is being paid to environmental contexts in which behaviors occur to account for health and behavioral disparities, as well as assessing the environment as a possible mediator of behavioral interventions (14–16). Few studies focus on patients with cancer or survivors. Consideration of the built environment may be even more salient for this population as cancer treatments may affect some functioning ability (17, 18), and thus make individuals more susceptible to environmental barriers to physical activity. Furthermore, very little is known about how built environment exposures may be moderating or mediating biological cancer risk factor mechanisms such as insulin resistance and inflammation, with only one study published that has assessed effects of built environment on insulin, but not in cancer survivors (19). Little is known about how engagement with

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environments that promote positive lifestyle behaviors impacts breast cancer survivors. Furthermore, there are currently no published studies on how built exposures influence biomarkers such as insulin and glucose in this population.

Of the studies conducted in the general population, results are mixed regarding the relationship of lifestyle behaviors like physical activity and diet with the walkability of a neighborhood, safety measured by crime rates, access to parks and recreation, greenspace, built food environment, and other environmental attributes (20–24). Inconsistency in results has been tied to a number of methodologic issues, one of which is the use of poor definitions of environmental exposure that lack specificity and variability (25, 26). The majority of studies that examine the relationship between environment and behaviors utilize a 400 m–2 km buffer around the home to define an individual's environment (27, 28). This static characterization of an individual's environment does not accurately reflect a person's daily mobility path and exposures, and severely limits the variance in exposures over the study data collection period as an individual visits various places. Furthermore, single location estimates of exposure underestimate associations when related to total behaviors, such as daily physical activity (29, 30). Global Positioning System (GPS) devices can obtain more accurate representations of a person's daily environmental exposure by recording latitude and longitude at varying time intervals (down to the second) while a person engages in their daily routine. Multiple studies have demonstrated the feasibility and utility of using GPS tracks to assess exposure (31), but research is ongoing about the best methods for extracting meaningful exposure measures from GPS data (25). In addition, there are no studies that compare how dynamic exposure measures compare to static measures in statistical models relating environment to health outcomes. Such comparisons are necessary to determine whether adding GPS logging devices to environment and health behavior studies is worth the additional cost of data collection and processing.

In this study, we conducted a novel analysis assessing how exposure to walkable and recreation environments is related to insulin resistance in a cohort of overweight and obese breast cancer survivors. We focus on insulin resistance [gauged using the homeostatic model assessment of insulin resistance (HOMA-IR; ref. 32)], which is reported to increase both the risk of incident and recurrent breast cancer by 2-fold (33, 34). In addition, HOMA-IR has been identified as a good model of insulin resistance for cohort studies, as it requires only a single plasma sample assayed for insulin and glucose (35). We define dynamic exposure by using a GPS-based Kernel Density Estimate (KDE) from the GPS points of participants. KDE is a method for smoothing point patterns into a generalized surface by applying a kernel function with specified search radius to each point in the data set, and is commonly utilized for GPS data in human and animal studies (36–38). We hypothesize that increased exposure to walkable and recreation environments will be associated with reduced insulin resistance, mediated through the pathway of physical activity (39, 40). Furthermore, we hypothesize that a dynamic GPS-based exposure measure using KDE will be better able to establish this association than a traditional, home-based static measure of exposure. This study was designed to contribute to gaps in the literature about (i) the effects of environments on insulin resistance in breast cancer survivors and (ii) our understanding of best exposure measurement methods for use in predictive models.

Materials and Methods

Study design and population

The Reach for Health (RfH) study was a randomized trial in overweight or obese women with a history of early-stage postmenopausal breast cancer conducted within the University of California San Diego (UCSD, California) Transdisciplinary Research in Energetics and Cancer program. The study used a 2 $\times$ 2 factorial design to assess how weight loss, metformin, or both influenced biomarkers associated with increased breast cancer mortality. The full study protocol is published in Patterson and colleagues (41). The RfH study obtained UCSD IRB approval and all participants provided written consent. RfH is registered in clinicaltrials.gov (NCT01302379).

In this study, we use RfH baseline data. Eligible participants for the study were overweight or obese women (BMI $\geq$ 25 kg/m^2) that had been diagnosed postmenopause with stage IA–IIIC primary operable breast carcinoma in the past 10 years, and were not currently undergoing chemotherapy or radiotherapy. Women were recruited from San Diego and Orange Counties between 2011 and 2015. In total, 333 women were recruited for the study. Women that were diabetic, using hormone replacement therapy, or had a condition that interfered with participation were excluded. Study measurements taken at baseline clinic visits included questionnaires, 7 days of wearing accelerometer and GPS sensors, physical measurements, and fasting blood draws. Of the 333 participants, baseline data from 249 women living in San Diego County were used for this study to geographically match women to our existing San Diego County-based GIS database for assessing environmental exposure. Women living outside of the County were excluded. The 249 women had an average age of 62.4 years (SD 7.2), average body mass index (BMI) of 30.7 kg/m^2 (SD 4.9), 9.6% were Hispanic, 67.9% were married, and 52.2% were employed.

Measurement

Participant measurements used in this study were collected at baseline. A fasting blood draw was collected in Ethylenediaminetetraacetic acid (EDTA) vacutainer tube. Plasma was isolated by centrifugation for 10 minutes at 4°C, and resulting plasma stored in 1.0-mL aliquots at −80°C. The primary biomarkers of interest for this study were insulin and glucose. Fasting plasma glucose concentrations were measured using a standard glucose oxidase method (YSI 2900 Bioanalyzer). Intra-assay coefficient of variance for glucose measurement was 3.2%. Fasting plasma insulin concentrations were determined by immunoassay (Meso Scale Discovery, catalog #K15164C). Intra-assay coefficient of variance for insulin measurement was 6.6%. HOMA-IR was calculated as described [glucose (mg/dL) $\times$ insulin (mU/L) divided by 405] (32). Mean HOMA-IR was 3.31 with a SD of 2.13, minimum of 0.51, and maximum of 13.50. Higher HOMA-IR values indicate increased insulin resistance, which is a feature of disorders like diabetes, obesity, hypertension, cancer, and autoimmune diseases.

Physical activity and location were measured with 7 days of a hip-worn accelerometer and GPS device. Participants wore Qstarz GPS devices (BT-Q1000XT) attached to a belt worn on the waist. A Qstarz logs geographic location coordinates, distance, speed, elevation, and time every 15 seconds. It has an industry reported

accuracy of 3 m, and independent validation has shown that median error of the device varies by behavior (from 3.9 m for walking to 0.5 m for driving) and environment (from 5.2 m in urban canyons to 0.7 m in open areas; ref. 42). Participants also wore a triaxial accelerometer (GT3X+, ActiGraph) worn on the same belt on the hip as the GPS. The ActiGraph yields valid estimates of physical activity in controlled and free-living environments, and has been validated in older adult populations (43, 44). If participants wore devices for less than 5 days with $\leq$600 minutes of wear time, they were asked to rewear the devices for the number of days needed plus one. Sensor data was collected within 2 weeks of clinical measurements, including blood specimen collection.

GPS data were processed and joined to the accelerometer data using the Personal Activity and Location Measurement System (PALMS; refs. 45, 46). Data were aggregated and merged at the minute level. Missing GPS data was imputed using a validated imputation algorithm (47). Accelerometer nonwear time was determined using a Choi algorithm in which 90 consecutive minutes of zero activity counts on the *x*-axis with a 2-minute spike tolerance was screened as nonwear (48, 49). After consideration of nonwear time and missing GPS data, valid wear days were defined as days with a minimum of 600 minutes with combined accelerometer and GPS data. For this study, activity was categorized into intensity–weighted categories of walking ($\geq$760 counts/minute) and not walking (<760 counts per minute) using thresholds applied in prior research for older adults (50–52).

Geographic Information System (GIS) data was downloaded from the San Diego Regional Planning Agency. Data ranged from 2012–2014 to best match the period of the baseline study data collection. Walkability was calculated on a 200 $\times$ 200m grid for all of San Diego County using the added z-scores of land use mix, intersection density, and residential density (53–55). Recreation Area was calculated by merging together recreational sites such as fitness business, school playgrounds, parks and recreation lands, bike paths, trails, areas around major streams and lakes, and beaches. Sites that were classified as points or lines were buffered by 100 m, and all areas were merged together to create a recreation area layer. The layer was converted to the 200 $\times$ 200m grid with proportion of recreation per grid unit calculated as a z-score. All z-scores were normalized to a 0–10 scale. All GIS analysis was performed in ArcMap 10.3. GPS, accelerometer, and GIS data were loaded into a HIPAA compliant PostgreSQL geodatabase to allow for rapid and secure analysis (56).

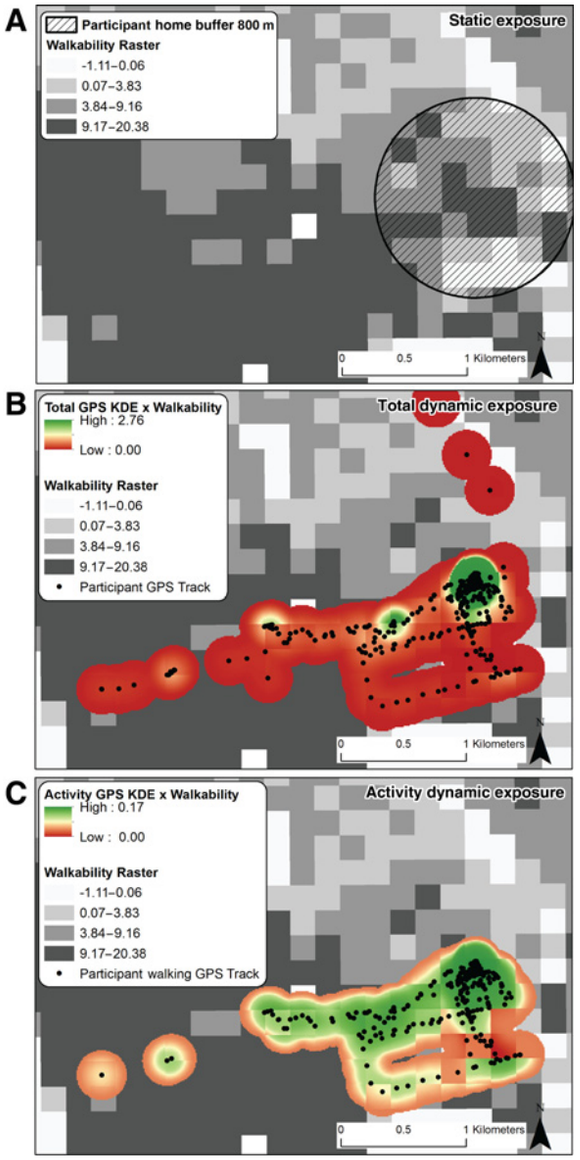

Figure 1.
Examples of the static (**A**), total dynamic exposure (**B**), and activity dynamic exposure (**C**) measures overlaid on the walkablity raster.

Statistical analysis

Home-based static measures of exposure were calculated with an 800 m circular buffer around each participant's home (Fig. 1A). Two buffer sizes were initially compared (800 and 1,600 m), and only minor difference in either environmental measures were found across the sample. The 800 m buffer was chosen as more representative of what was accessible directly around the home. Walkability and Recreation Area scores of raster cells that intersected with the buffer were added to a single value of Walkability and Recreation Area exposure for each participant. GPS-based dynamic measures of exposure were calculated with the KDE tool in ArcGIS. All GPS points for the entire participant's wear time were used to create a total exposure surface (Fig. 1B). KDE in ArcGIS utilizes a quartic kernel function (57). Bandwidth of the search radius was set to 200 m to keep the density estimate relatively tightly aligned with the original GPS track. The resulting KDE surface was then multiplied by the walkability and recreation area rasters to obtain Walkability and Recreation Area dynamic exposure measures. In addition to the total wear time dynamic exposure measure, an activity-based dynamic exposure measure was also created. This was of interest to assess if there was a difference in effects of exposure during all times the participant wore the device (including when they were not moving) as compared with exposure during behaviors relevant to the outcome of insulin resistance (such as walking or physical activity). GPS points for times when the participant was walking as measured by $\geq$760 counts per minute with the accelerometer were extracted from the participant's total GPS dataset, and the KDE

Table 1. Exposure measures, definitions, and method of calculation

Exposure measure	Definition	Method of calculation
Walkability: Static	Walkability of the 800 m area around the participant's home.	Home 800 m buffer multiplied by walkability raster.
Walkability: Total Dynamic	Walkability of the 200 m area around the participant's daily movement, weighted by density of GPS points in any given location.	KDE of all participant GPS points multiplied by walkability raster.
Walkability: Activity Dynamic	Walkability of the 200 m area around the participant's daily physical activity, weighted by density of physical activity GPS points in any given location.	KDE of all participant physical activity GPS points multiplied by walkability raster.
Recreation Area: Static	Recreation area in the 800 m area around the participant's home.	Home 800 m buffer multiplied by recreation area raster.
Recreation Area: Total Dynamic	Recreation area in the 200 m area around the participant's daily movement, weighted by density of GPS points in any given location.	KDE of all participant GPS points multiplied by recreation area raster.
Recreation Area: Activity Dynamic	Recreation area in the 200 m area around the participant's daily physical activity, weighted by density of physical activity GPS points in any given location.	KDE of all participant physical activity GPS points multiplied by recreation area raster.

procedure was performed on only those points (Fig. 1C). Table 1 provides the name and definition of each exposure measure.

A linear regression model was employed to model the relationship between insulin resistance and environmental exposures where the outcome was HOMA-IR. Covariates were age, BMI, and average daily wear time of devices for models that included KDE measures. Separate models tested each independent variable Walkability: Static, Walkability: Total Dynamic, Walkability: Activity Dynamic, Recreation Area: Static, Recreation Area: Total Dynamic, Recreation Area: Activity Dynamic.

Results

Descriptive measures of exposure to Walkability and Recreation Area for each of the exposure types (static, total dynamic, and activity dynamic) are shown in Table 2. For Walkability, the total dynamic exposure measures had the largest mean values and greater SDs and range than the static or activity dynamic exposure measures. The Walkability activity dynamic measure had the smallest mean and range. For Recreation Area, the static and total dynamic measures had almost the same mean values; however the SD of the total dynamic measure was much larger than the static measure. The Recreation Area activity dynamic measure had the lowest mean, standard deviation, and range.

Regression results are shown in Table 3. R^2 values for all models were in the range of 0.40–0.45, with values highest for models that included the total dynamic independent variables. Age was not significantly associated with HOMA-IR in any model, whereas BMI was a highly significant ($P < 0.001$) predictor of higher insulin resistance in all models. Wear time was significant for all dynamic models ($P < 0.05$). There was no association of the static or total dynamic Walkability and Recreation Area exposures with HOMA-IR. Activity dynamic measures for both Walkability and Recreation Area was associated with lower HOMA-IR ($P < 0.05$), indicating that increased exposure to Walkable and Recreation supportive environments during physical activity was associated with decreased insulin resistance.

Discussion

Results show that exposure measured with GPS data can provide more variability in a study population when compared with the traditional home-based static measures of exposure, and can also provide researchers with the opportunity to examine exposure during specific behaviors or activities. As individuals move through their environments, they accumulate a wider range of exposures than what would be captured solely around their homes. This increased variance in GPS exposure may allow researchers to employ their efforts in the data processing stage, rather than at the recruitment stage through restricted sampling strategies as the exposure variability can be maximized because of the participant's movement. Furthermore, by allowing environmental exposure to be assessed during specific activities, a more precise measure of exposure can be obtained on the basis of the behavior of interest.

Compared with static measures, the total dynamic (GPS-based KDE) measures captured more variation in exposure to Walkable and Recreation Area built environments. These findings may have important implications for the design of studies that seek to understand effects of environment on health outcomes. A major problem for such studies is lack of variability in environmental exposures: because environmental effects are often small compared with individual effects, large variability in exposure to environment is important to detect effects. However many studies are conducted in one city with limited variability in built environment, and participants are rarely sampled to maximize variability of home location. Efforts to design studies with proper environmental variability can take significant resources for recruiting from specific neighborhoods or census tracks, or including multiple cities and countries, as was done in the International Physical Activity and Environment Network (IPEN) studies (58, 59). The variation in exposure to Walkable and Recreation environments was reduced when limiting dynamic exposure to points when a participant was engaging in physical activity. This is due to the increased specificity of measuring exposure only during physical activity, a technique which may be of interest to studies

Table 2. Descriptive measures of environmental exposure measures in a study of 249 overweight/obese, postmenopausal breast cancer survivors

Environment exposure	Mean (SD)	Minimum	Maximum
Walkability: Static	68.3 (30.76)	10.46	225.35
Walkability: Total Dynamic	83.90 (51.61)	8.97	295.35
Walkability: Activity Dynamic	4.19 (3.83)	0.25	32.80
Recreation Area (km^2): Static	300.10 (114.89)	0.00	623.44
Recreation Area (km^2): Total Dynamic	300.17 (240.73)	13.02	1654.21
Recreation Area (km^2): Activity Dynamic	17.21 (17.40)	0.59	168.98

Table 3. Standard coefficients from regression models[a] of the association of six built exposure measures (independent variables) with HOMA-IR in a study of 249 overweight/obese, postmenopausal breast cancer survivors

Variable	IV: Walkability Static β (SE)	IV: Walkability Total Dynamic β (SE)	IV: Walkability Activity Dynamic β (SE)	IV: Recreation Area Static β (SE)	IV: Recreation Area Total Dynamic β (SE)	IV: Recreation Area Activity Dynamic β (SE)
Age	−0.005 (0.017)	−0.001 (0.018)	−0.005 (0.018)	−0.005 (0.017)	−0.001 (0.018)	−0.005 (0.018)
BMI	0.173 (0.025)[b]	0.173 (0.026)[b]	0.171 (0.026)[b]	0.172 (0.25)[b]	0.174 (0.026)[b]	0.171 (0.026)[b]
Wear time		−0.004 (0.002)[c]	−0.004 (0.002)[c]		−0.004 (0.002)[c]	−0.004 (0.002)[c]
Built exposure	0.001 (0.004)	0.000 (0.003)	−0.058 (0.033)[d]	−0.001 (0.001)	−0.000 (0.001)	−0.013 (0.007)[d]
R^2	0.399	0.428	0.440	0.400	0.429	0.440

[a]Each built environment exposure variable is modeled separately.
[b]$P < 0.001$.
[c]$P < 0.01$.
[d]$P < 0.05$.

looking to assess if particular behaviors are occurring in or being influenced by certain environments.

Active dynamic exposure measures were significantly associated with lower HOMA-IR, whereas the static and total dynamic measures were not. This result indicates that specificity of both the behavior and environment of interest may play an important role in examining associations between health and environment (26). Utilizing total GPS tracks to assess exposure may not be specific enough: the total exposure measure accounts for all exposures a participant encounters throughout their day including the environment around them when they are indoors at work or home. With the KDE measure, this may become problematic as the kernel weights areas where significant time is spent more heavily than places where little time is spent. Therefore, exposure while a participant spends hours inside their work or home becomes more heavily weighted than exposure while a participant is out walking. To assess if limiting exposure to times when a participant was engaged in physical activity is more relevant for HOMA-IR than total exposure, we calculated the activity exposure measure using only GPS points that had accelerometer activity of 760 or greater. This behavior-specific measure was significantly associated with HOMA-IR, whereas the total dynamic measure was not, indicating the importance of ensuring that environmental exposure measures are accurately specific to the behavior of interest.

One major concern with using KDE and GPS tracks to measure exposure, is "selective daily mobility bias," which has been identified as a significant source of confounding for environment-health studies that account for daily mobility (60). The concern is that people who are active often seek out specific types of environments in which to be active, thus biasing any measured relationships between an environment and a behavior. Selective daily mobility bias was raised in GPS studies as authors appeared to claim that GPS data strengthened the evidence for causal associations. In this cross-sectional analysis, we do not claim any causal relationship. Future analyses will assess the effects of dynamic exposure and changes in dynamic exposure on the RfH intervention outcomes to explore how exposure to certain environments may play a mediating role in intervention outcomes. Of interest regarding mobility bias is the question of how the bias plays out when the outcome measure is not a physical activity behavior, but rather a biomarker. In this regard does it matter if a woman is influenced by her environment to spontaneously participate in more walking, or if she actively seeks out walkable environments? The activity dynamic measure controls for amount of physical activity each participant engages in, and findings suggest that women who engage in physical activity in more walkable and recreation supportive environments are seeing lower insulin resistance. It will take further analysis to untangle how much the behavior (walking and PA) as compared with the environment the behavior is in plays a role in influencing insulin resistance, or other biomarkers.

The regression results showed that for this sample of cancer survivors, activity dynamic exposure to Walkability and Recreation Areas was significantly associated with lower levels of HOMA-IR. This result suggests that for cancer survivors, physical activity in more walkable or recreation-supportive areas is associated with reduced insulin resistance and cancer recurrence risk. This is an important result to consider for future community advocacy efforts that support built environmental changes. It also has important implications for planning lifestyle interventions with breast cancer survivors. Women living and engaging in built environments that are less supportive of positive lifestyle behaviors may need more assistance in achieving desired intervention results.

In summary, this study provides evidence for the benefits of using GPS-based dynamic exposure measures over traditional home-based static measures for associating built environment exposure to health outcomes. These measures offer greater variability in built environment exposures among a study population, and are also more accurate in their representation of the built environments that individuals encounter in their daily lives. The study also offers evidence for the link between exposures to lifestyle supportive environments and reduced insulin resistance in breast cancer survivors. This finding has important implications for designing community and individual level interventions that can address cancer risk inequities that arise from the environments in which breast cancer survivors live and engage.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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