Dissecting the causal question underlying the association between cancer and ADRD: an opportunity to understand sources of bias

1. Introduction

Many observational studies have consistently found that individuals with cancer have a lower risk of developing of Alzheimer´s disease or related dementias (ADRD) when compared to individuals with no history of cancer (Ma et al. 2014; Hanson et al. 2016; van der Willik, Schagen, and Ikram 2018; Ospina-Romero et al. 2020). These findings have motivated substantial research toward mechanistic explanations, including searching for and hypothesizing that molecular and genetic mechanisms may explain this association(Behrens, Lendon, and Roe 2009; Harris, Tindale, and Cumming 2014; Nudelman et al. 2019; Papin and Paganetti 2020; Jane A. Driver 2014; Olson and Marks 2019; Li et al. 2021; Jane A. Driver, Zhou, and Lu 2015). These research inquiries inevitably lead to discussions of repurposing or augmenting current cancer chemotherapeutics for ADRD (Snyder et al. 2017).

Nevertheless, inferring any treatment or mechanistic effects from the observed cancer-ADRD inverse association is not straightforward. Researchers have raised concerns related to the competing event of death, unmeasured confounding, and ascertainment error that could explain these results(Jane A. Driver 2014; Ganguli 2015). However, understanding these or other sources of bias first requires making explicit the causal question. Moreover, making explicit the causal question is one step toward tying a research study to a question that is relevant to decision-making(Didelez 2016; Labrecque and Swanson 2017).

To illustrate the complexities of inferring hypothetical or available treatments' effects on ADRD from the observed cancer-ADRD association, we focus on a specific question conceptualizing the Pin1 enzyme as the target of intervention. Previous animal studies have shown that Pin1 enzyme over-expression promotes tumorigenesis, while its down-regulation is attributed to mechanisms that contribute to neurodegeneration and amyloid deposition(Jane A. Driver, Zhou, and Lu 2015; Angelucci and Hort 2017; Li et al. 2021). If we one day could develop a drug that increases Pin1 expression specifically in brain tissue in hopes of preventing dementia, we could pose the question as: *What is the effect of this Pin1-targeting drug on the risk of ADRD over time compared to standard treatments?*

To explore how we might learn about this effect using real-world data on cancer and ADRD, we progressively build a causal directed acyclic graph to connect this particular causal question to the observable data and the assumptions we rely on to study the effect. We exemplify different scenarios with data collected from the Rotterdam Study, a population-based cohort study. We describe the challenges and how they translate into the analytic decisions. Last, we discuss how information on mortality and cause of death can provide insight about the direction of some sources of bias.

2. Overview of the causal structure

If this hypothetical Pin1-targeting drug was developed, the best way to understand its effect on dementia risk would be to have a well-conducted randomized trial in which we randomize eligible participants in late midlife (e.g., ages 50-60 years) to receive this drug or not, and closely monitor ADRD over a lengthy follow-up. Since this drug is not currently available, at best we can use observational data on Pin1 expression measurements. For example, suppose that a biomarker test was available to measure Pin1 and we measured this biomarker from (stored) baseline blood samples in a population based-cohort that recruited participants in late midlife.

In the observational setting, confounding could explain the observed association between Pin1 and ADRD. In the directed acyclic graph (Miguel A. Hernán and Robins 2020) of Figure 1, we present Pin1 expression measured at time t as P_{t-1} and ADRD diagnosis over time as Y_{t+1}. Both nodes may share causes L, and to assess the causal relationship between P_{t-1} and Y_{t+1} we would require adjusting for L. Previous studies have described age, sex, educational level and race/ethnicity as the minimal adjusting set of covariates(Ospina-Romero et al. 2020). However, environmental and behavioral factors such as smoking, which are known to cause microenvironmental changes such as inflammation and changes in tissue remodeling, may translate into Pin1 over-expression and are also related to the development of ADRD[ref].

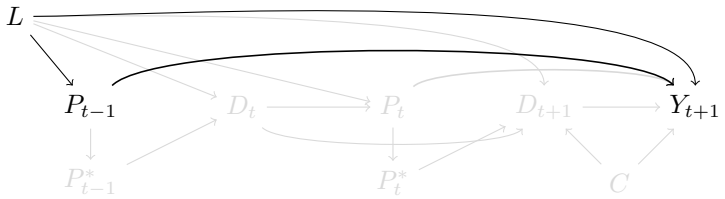


Figure 1: Pin1 as biomarker and risk of dementia

Currently, Pin1 expression is not an available biomarker for population-based research, so at best we can only rely on a proxy for it. Because Pin1 over-expression is present in tumors, and tumors are only measured through diagnosis, previous studies have considered Pin1 over-expression as the explanation behind the inverse association between cancer diagnosis and ADRD, though Pin1 was not explicitly part of the research question(Ospina-Romero et al. 2020; J. A. Driver et al. 2012; Musicco et al. 2013; Freedman et al. 2016; Bowles et al. 2017; Frain et al. 2017; Schmidt et al. 2017; Sun et al. 2020; Ording et al. 2020). Unlike measuring Pin1 at the same time to all participants (thought this would not necessarily mean this would be the ideal time to measure it, we discuss this point further in the discussion section), cancer diagnosis is a collected over time. We depict this feature in Figure 2, where P^*_{t-1} and P^*_t represent *cancer diagnosis* over time, the measured proxy of P_{t-1} and P_t respectively. Although this means we would measure the association between cancer diagnosis over time and ADRD in the observed data, we are assuming that the captured effect is only through the pathway that involves Pin1 expression over time.

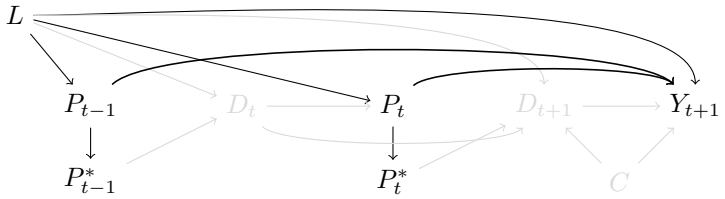


Figure 2: Cancer diagnosis as proxy for Pin1 expression

A challenge that arises by defining cancer diagnosis as the proxy for Pin1 is defining the time zero, the time where follow-up and screening for ADRD would begin after having the exposure measured. The eligibility criteria to join the study may not align with the time cancer diagnosis is measured. This situation may introduce inmortal-time bias (Miguel A. Hernán et al. 2016). For example, a study performed using data from the Framingham study (J. A. Driver et al. 2012) defined the exposed group with cancer as those participants with prevalent or incident cancer diagnosis (alternatively defined as "ever cancer" (Hanson et al. 2016)). This meant that a participant who had cancer diagnosis over follow-up contributed all their person-time to the cancer arm, including the time prior to the cancer diagnosis. By defining the exposure after the time of inclusion to the cohort, only participants who remain alive and free of ADRD diagnosis over follow-up can be defined as "ever cancer" Miguel A. Hernán et al. (2016).

This problem is avoided by recognizing the time-varying nature of cancer diagnosis. Several studies have considered cancer diagnosis as a time-dependent exposure. In this way, the time prior to cancer diagnosis

is allocated to the non-exposed arm, and the time after cancer diagnosis to the exposed arm (White et al. 2013; Hanson et al. 2016; Bowles et al. 2017). The price we pay with this approximation is that implicitly, this means that Pin1 would over-express at the time of cancer diagnosis, which is biologically implausible. Moreover, cancer diagnosis will only be measured in the subset of participants who are alive over follow-up. Thus we included death prior to cancer diagnosis as D_t and an arrow between D_t and P_t that represents a deterministic association such as that P_t is only observed if D_t is zero in Figure 3. In addition, we added an arrow between L and D_t, since covariates such as smoking may affect Pin1 over-expression but also affect the risk of death due to other causes such as COPD. Although L is time-varying in nature, we only depict L at one time-point for readability.

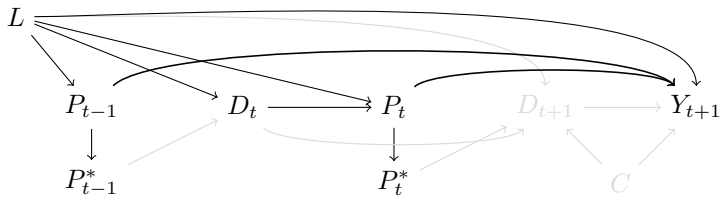


Figure 3: Time-varying cancer diagnosis and inmortal-time bias

We now move to the challenge of death as a competing event for ADRD, represented in Figure 4. For interpretability we exclude the time-varying process of cancer diagnosis and focus on Pin1 (and cancer diagnosis) as it had been measured in all participants at t. Given that some participants may die prior to having a cancer diagnosis over follow-up, we can only have ADRD over follow-up in the individuals who survive long enough to have an ADRD diagnosis. In the causal diagram of Figure 4 we include a node for death after the exposure P^*t has been measured, represented as D_{t+1}, this acts as a competing event of Y_{t+1} because if a participant dies by $t+1$, the participant cannot subsequently develop dementia. Furthermore, since D_{t+1} and Y_{t+1} are events related to aging and its consequences, C represents the shared causes of both events such as cardiovascular conditions. We also include an arrow between L and D_{t+1} following the argument discussed previously.

In the setting where P_t represented the targeted-drug for Pin1, and if this drug had no systemic beneficial or harmful side-effects such as that there is no arrow between P and D_{t+1}, a total effect would quantify the effect of P_t on Y_{t+1} that does not include any pathway mediated through D_{t+1}(Young et al. 2020). However, in the context of cancer diagnosis as the proxy for Pin1 over-expression, we cannot rule out the effect of cancer diagnosis on death, represented as the arrow between P_t^* and D_{t+1}. In this setting, a total effect of P_t in Y_{t+1} would include the causal pathway mediated by the effect of cancer diagnosis in mortality, which may translate into an inverse association(Young et al. 2020).

To isolate the direct effect of P_t in Y_{t+1} through measurement of P_t^* we have at least two alternatives of causal questions we can ask. We can either imagine a causal question where we decompose the effect of cancer by the different mechanisms that affect dementia and death separately(Stensrud et al. 2020). Alternatively, we can define an scenario where death could have been prevented. The latter is defined as the controlled direct effect, where death is considered as a censoring event and it relies on the assumption that we have measured all C to block the pathway $Y_{t+1} \leftarrow C \rightarrow D_{t+1} \rightarrow P_t^* \rightarrow P_t$. Previous studies have defined death as a censoring event [], although failed to explicitly define how to comply with the independent censoring assumption. Moreover, adjusting for confounders for dementia (such as only adjusting for L) may represent partially the adjustment for the competing event of death (**geskus?**), to block the pathway mediated by C we need to consider covariates that change over time and that affect both nodes, such as cardiometabolic conditions.

To summarize, the complexity of the causal structure that describes the effect of Pin1 through the proxy of cancer diagnosis in the risk of ADRD illustrate the potential sources of bias, as observed in Figure 5. Even so, this is a simplified version since we omitted other sources of measurement error (Miguel A. Hernán and Robins 2020) and the time-varying nature of all nodes and feedback loops between them which would further complicate interpretability and identificability.

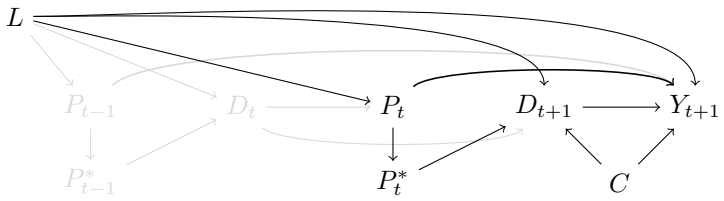


Figure 4: Death as a competing event

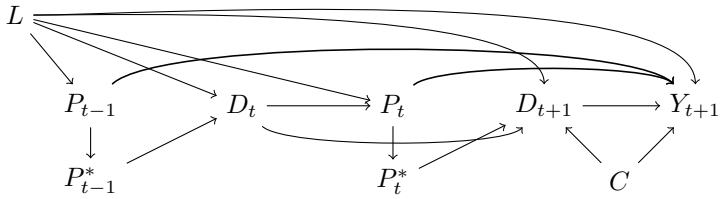


Figure 5: Direct effect of Pin1 in the risk of ADRD

We now turn to an application where we show how these challenges translate in analytic decisions, and we will show ways to mitigate or better understand to the best of the available data's abilities. Nevertheless, we acknowledge that cancer diagnosis represents a complex and heterogenous health condition that exceeds the representation of Pin1 expression, thus, at best we may test the sharp null hypothesis rather than estimating the causal effect of Pin1. In this section we conduct an analysis of the cancer-ADRD association that is structured to the best of the available data's abilities to inform the possible effect of Pin1 on all cause-dementia.

3. Application to the Rotterdam Study

We use data collected in the Rotterdam Study, a population-based prospective cohort study among persons living in the Ommoord district in Rotterdam, the Netherlands. Recruitment and initial assessments were held between 1990 and 1993; it was later extended between 2000 and 2001 consisting of individuals who had reached the age of 55 years or who had moved into the study area. Participants from first subcohort had follow-up visits between 1993-1995, 1997-1999, 2002-2005, and 2008-2010, second subcohort had follow-up visits between 2004 and 2005, and between 2011 and 2012(Ikram et al. 2020). All participants had data on incident cancer diagnosis and incident dementia diagnosis through follow-up, collected from medical records of general practitioners (including hospital discharge letters) and through linkage with national registries. Date and cause of death was collected on a weekly basis via municipal population registries. Data on clinical outcomes was available until 2015.

We considered as inclusion criteria being between 60 and 70 years old at study entry, without history of cancer diagnosis, free of cognitive decline or with previous history of dementia. Out of 10998 persons who participated at study entry, 3642 were considered eligible. Time to cancer diagnosis, time to dementia diagnosis and death status was measured for all participants. All participants were followed from study entry until dementia diagnosis, death or 20 years after their individual baseline date, whichever occurred first.

3.1. Methods

We illustrate the association between cancer and dementia diagnosis under two scenarios. Scenario A replicates the setting that defines cancer proxy as *"cancer ever vs. never"* (J. A. Driver et al. 2012). Scenario

B defines cancer diagnosis is a time-varying exposure. To address confounding we fit inverse probability treatment weights, stabilized and truncated at 99th percentile. In scenario A, weights were defined as the inverse of the probability of cancer diagnosis conditional on baseline covariates such as age at study entry, sex, educational attainment, cohort, smoking status. In contrast, for scenario B weights were defined to represent the product of the inverse probability of being diagnosed with cancer over time, conditional on time-varying covariate history. This recreates a pseudopopulation in which time-varying covariates do not predict the risk of cancer diagnosis at time t (M. Á. Hernán, Brumback, and Robins 2000). Time varying covariates included age at study entry, sex, ApoE4 status, educational attainment and the time-varying covariates such as smoking status, systolic blood pressure, BMI and prevalent and incident comorbidities such as: hypertension and diabetes. Further details on modeling specifications and weights assessment are presented as **Supplementary material x**.

Inverse probability censoring weights for death were calculated to relax the independent censoring assumption. In scenario A, weights represent the inverse of the probability of not dying conditional on baseline covariates such as age, educational attainment, ApoE4, and baseline measurements of smoking status, hypertension status, systolic blood pressure, BMI, history of diabetes and cohort. For individuals who died, their censoring weight is zero (Miguel A. Hernán and Robins 2020). In scenario B time-varying weights represent the product of the inverse probability of surviving in each year prior to t, conditional on the measured shared causes of death and dementia. For an individual who has died by time t, the year t censoring weight is zero. Weights were fitted including the same covariates used to estimate weights for time-varying cancer diagnosis, though we additionally added time-varying cancer, stroke, and heart disease diagnosis as predictors for death.

To estimate the controlled direct effect of Pin1 in the risk of ADRD, we compared the complement of a weighted Kaplan-Meier survival estimator for participants who developed cancer versus those who did not, with time indexed in years. The weights are time-varying by follow-up year, defined as a product of the year-specific inverse probability of treatment weights and the inverse probability of censoring by death weights. Estimates of the controlled direct effect at 20 years of follow-up are presented as risk differences (RD) and risk ratios (RR). All 95% confidence intervals were calculated using percentile-based bootstrapping based on 500 bootstrap samples.

For illustrative and comparative purposes we calculated hazard ratios (HR). Hazards, unlike risks, inherently condition on surviving both dementia and death, as such they will not have a causal interpretation in this case (Young et al. 2020). We additionally calculated the controlled direct effect considering death as an unconditional independent censoring event (as if there were no arrows from C to D_{t+1} and Y_{t+1}).

Since the conditional independent censoring assumption is untestable, we compute Peterson upper and lower bounds (Peterson 1976) to represent: 1) the extreme scenario of independence, that refers to an scenario were those who died would never develop dementia (lower bound) and 2) complete dependency, that refers to an scenario where those who died would have a dementia prior to death (upper bound). The lower bound is calculated with the Aalen-Johansen estimator treating death as a competing event, and the upper bound is calculated with the Kaplan Meier estimator for the combined outcome of dementia or death.

All analysis were performed using R, code is provided in supplementary material and available in https://github.com/palolili23/2021_cancer_dementia.

3.2. Results

Participants had a mean age of 64.46 (SD: 2.86), and 54% (n = 1981) were women. Further details on participants are presented in Table 1. Over follow-up, 24% (n = 878) developed cancer and 76% (n = 2764) remain free of cancer diagnosis, the median age of cancer diagnosis was 73 (IQR: 69-77). From the total sample, 12% (n = 431) had dementia over follow-up and median time to dementia was 79 (IQR: 75-83). Among participants with incident cancer, 6% (n = 50) had dementia diagnosis and 63% (n = 549) died over follow-up, 32% (n = 279) remain alive at 20 years since study entry. In contrast, among participants free of cancer diagnosis over follow-up, 14% (n = 385) were diagnosed with dementia and 23% (n = 624) died

over follow-up, 63% (n = 1755) were alive at the end of follow-up. Figure x. shows the magnitude of the proportion of people who died over time.

Results for all scenarios are present in Table 2. Had we defined the proxy for Pin1 as *ever cancer*, and relying on death as independent censoring event (unconditional), we observe a significant protective effect of ever having cancer in the risk of dementia [RR: 0.7 (0.49,0.93), HR: 0.54(0.4,0.74)]. This effect did not change after including censoring weights for death [RR: 0.72 (0.51,0.96); HR: 0.55(0.4,0.74)].

In contrast, had we defined cancer diagnosis as a *time-varying* proxy for Pin1 over-expression and had we prevented death conditional on covariates, the risk of dementia had participants had a cancer diagnosis over time is higher [RR: 1.1 (0.86,1.39); HR: 1.09(0.78,1.51)], though confidence intervals cross the null.

Tables

Table 1: Descriptive characteristics of individuals who had a cancer diagnosis and of those free of cancer diagnosis over follow-up.

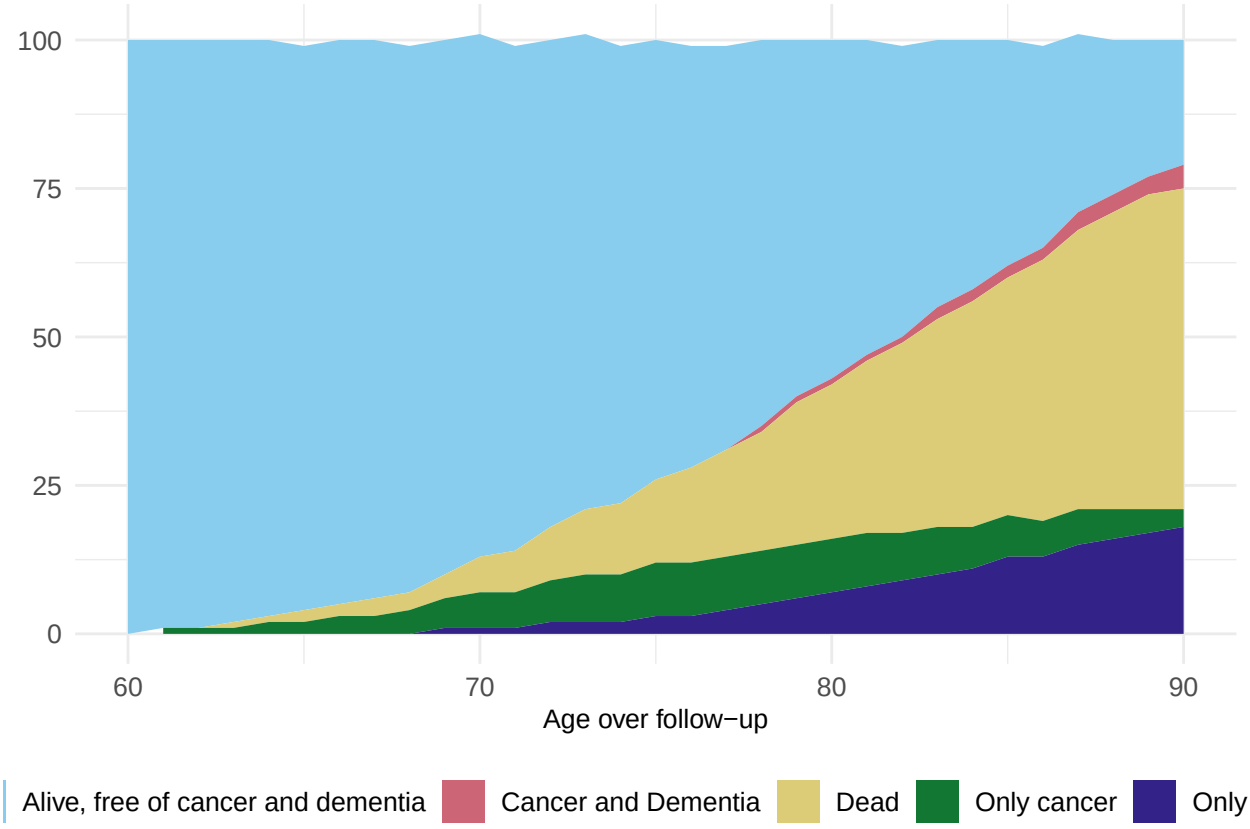
	Incident cancer	No incident cancer
n	878	2764
sex = Male (%)	520 (59.2)	1141 (41.3)
age_0 (mean (SD))	64.61 (2.87)	64.42 (2.86)
education (%)		
Higher	114 (13.0)	269 (9.7)
Intermediate	412 (46.9)	1225 (44.3)
Lower	347 (39.5)	1251 (45.3)
Unknown	5 (0.6)	19 (0.7)
apoe4 (%)		
Not carrier	622 (73.8)	1874 (71.1)
One allele carrier	203 (24.1)	685 (26.0)
Two allele carrier	18 (2.1)	78 (3.0)
smoke1 (%)		
Current	260 (29.6)	664 (24.0)
Former	425 (48.4)	1301 (47.1)
Never	193 (22.0)	799 (28.9)
bmi1 (mean (SD))	26.39 (3.50)	26.65 (3.80)
oh1 (mean (SD))	13.25 (17.97)	10.13 (15.50)
sbp1 (mean (SD))	138.74 (20.98)	138.67 (20.80)
ht1 = No history of hypertension (%)	369 (42.0)	1141 (41.3)
hd_prev = No history of heart disease (%)	800 (92.6)	2503 (92.5)
hd_v = No incident heart disease (%)	665 (75.7)	1967 (71.2)
diabetes_prev (%)		
History of diabetes	91 (10.4)	284 (10.3)
No history of diabetes	553 (63.0)	1981 (71.7)
Unknown	234 (26.7)	499 (18.1)
diab_v = No incident diabetes (%)	713 (81.2)	2215 (80.1)
stroke_prev = No history of stroke (%)	863 (98.3)	2717 (98.3)
stroke_v = No incident stroke (%)	777 (88.5)	2403 (86.9)
cancer_v = No incident cancer (%)	0 (0.0)	2764 (100.0)

Table 2. Risk difference and risk ratio for the risk of dementia

Proxy	model	Risk Difference	Risk Ratio	Hazard Ratio
Ever vs. never	Unadjusted	-5.9 (-10.4,-1.1)	0.71 (0.49,0.95)	0.55(0.41,0.73)
Ever vs. never	IPTW + IPCW	-6.3 (-11.3,-1)	0.72 (0.51,0.96)	0.55(0.4,0.74)
Ever vs. never	IPTW	-6 (-10.6,-1.4)	0.7 (0.49,0.93)	0.54(0.4,0.74)
Time-varying	Unadjusted	-0.6 (-4.1,3.9)	0.97 (0.8,1.21)	0.98(0.73,1.32)
Time-varying	IPTW	-0.8 (-4.4,4)	0.96 (0.78,1.21)	0.97(0.71,1.31)
Time-varying	IPTW + IPCW	2 (-2.9,7.6)	1.1 (0.86,1.39)	1.09(0.78,1.51)

Figures

Figure 1: Distribution of participants under each health status, by age over follow-up



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