Estimating the Causal Effect of an Exposure on Change from Baseline Using Directed Acyclic Graphs and Path Analysis

Benoît Lepage,[a,b,c] *Sébastien Lamy,*[a] *Dominique Dedieu,*[a] *Nicolas Savy,*[a,b,d] *and Thierry Lang*[a,b,c]

Abstract: When estimating the causal effect of an exposure of interest on change in an outcome from baseline, the choice between a linear regression of change adjusted or unadjusted for the baseline outcome level is regularly debated. This choice mainly depends on the design of the study and the regression-to-the-mean phenomena. Moreover, it might be necessary to consider additional variables in the models (such as factors influencing both the baseline value of the outcome and change from baseline). The possible combinations of these elements make the choice of an appropriate statistical analysis difficult. We used directed acyclic graphs (DAGs) to represent these elements and to guide the choice of an appropriate linear model for the analysis of change. Combined with DAGs, we applied path analysis principles to show that, under some functional assumptions, estimations from the appropriate model could be unbiased. In the situation of randomized studies, DAG interpretation and path analysis indicate that unbiased results could be expected with both models. In the case of confounding, additional (and sometimes untestable) assumptions, such as the presence of unmeasured confounders, or effect modification over time should be considered. When the observed baseline value influences the exposure ("cutoff designs"), linear regressions adjusted for baseline level should be preferred to unadjusted linear regression analyses. If the exposure starts before the beginning of the study, linear regression unadjusted for baseline level may be more appropriate than adjusted analyses.

(*Epidemiology* 2015;26: 122–129)

In clinical epidemiology, we sometimes need to estimate the effect of an exposure of interest E (eg, an antihypertensive treatment) on change from baseline of a time-dependent quantitative outcome (eg, blood pressure at time t, denoted as $BP(t)$). The exposure E is observed at the beginning t_1 of the study (although it may have occurred before the beginning of the study), and a change score is defined as the difference ΔBP in blood pressure between the beginning t_1 and the end t_2 of the study:

$$\Delta BP = BP(t_2) - BP(t_1)$$

Two methods of estimating the effect of E on change from baseline have been regularly discussed: computing a linear regression of ΔBP adjusted for baseline value $BP(t_1)$ (sometimes called analysis of covariance, when the exposure of interest is categorical) or unadjusted for baseline value (sometimes called "simple analysis of change score").[1] For the individual person i ($i = 1, \ldots, I$), the linear regression of ΔBP on E adjusted for $BP(t_1)$ is as follows:

$$\Delta BP_i = \mu + \tau_{BP1} BP_i(t_1) + \tau_E E_i + \varepsilon_i \quad (1)$$

It is known that the regression coefficient τ_E can also be estimated using a linear regression of $BP(t_2)$ on E adjusted for $BP(t_1)$:[2]

$$BP_i(t_2) = \mu + (\tau_1 + 1) BP_i(t_1) + \tau_E E_i + \varepsilon_i$$

The linear regression of ΔBP on E unadjusted for $BP(t_1)$ is as follows:

$$\Delta BP_i = \mu' + \tau_E' E_i + \varepsilon_i' \quad (2)$$

The causal effect of E on ΔBP is estimated by the regression coefficients τ_E or τ_E' according to the model chosen. In some situations, the models can lead to very different results. This

Submitted 15 October 2012; accepted 30 June 2014; posted 14 November 2014.
From the [a]Inserm UMR1027, Toulouse, France; [b]University of Toulouse III, UMR1027, Toulouse, France; [c]Department of Epidemiology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; and [d]Toulouse Institute of Mathematics, UMR C5583, Toulouse, France.
Supported by the following institutions, as part of the IReSP (Institut de Recherche en Santé Publique) 2010 call for projects: la Direction Générale de la Santé (DGS), la Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS), le Régime Social des Indépendants (RSI), la Caisse Nationale de Solidarité pour l'Autonomie (CNSA), la Mission Recherche de la Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques (MiRe-DREES), l'Institut national de prévention et de promotion de la santé (Inpes).
SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com). This content is not peer-reviewed or copy-edited; it is the sole responsibility of the author.
The authors report no conflicts of interest.
Correspondence: Benoît Lepage, Inserm UMR1027, 37 allées Jules Guesde, F-31062 Toulouse, France. E-mail: benoit.lepage@univ-tlse3.fr.

ISSN: 1044-3983/15/2601-0122
DOI: 10.1097/EDE.0000000000000192

paradox was pointed out by Lord[3] in the case of a nonrandomized study exploring the effect of sex on weight change.

In the literature, the choice between a model adjusted or unadjusted for the baseline value of the outcome is usually based on considerations about the design of the study and the regression-to-the-mean phenomena. Regarding study design, Van Breukelen showed that, compared with linear regressions of ΔBP unadjusted for $BP(t_1)$, adjusting for $BP(t_1)$ provides more power in randomized studies but may be more biased in nonrandomized studies.[4] Senn also showed the value of adjusting for baseline outcome level to obtain unbiased estimates of the exposure in randomized studies as well as in "cutoff designs" (studies in which subjects are allocated to one of the exposure groups according to their baseline value). In addition, he stated that in observational studies where baseline values are different between exposure groups, both adjusted and unadjusted models for $BP(t_1)$ would probably give biased results.[1]

This regression-to-the-mean phenomenon results from intraindividual variability and measurement error on the baseline outcome value (a short illustration is given in the eAppendix; http://links.lww.com/EDE/A839).[5,6] Based on directed acyclic graphs (DAGs) and in the case of a nonrandomized study, Glymour et al[7] showed that adjusting for baseline outcome level could lead to a biased estimate when the outcome is measured with error, whereas models unadjusted for baseline level could give unbiased results. Van Breukelen[4] indicated that in the case of "cutoff design" studies, regression-to-the-mean results in a spurious association between the exposure and change from baseline, which is correctly controlled by adjusting for baseline value, but is ignored with unadjusted linear regressions. On the contrary, in nonrandomized studies with baseline values that differ between preexisting exposure groups, there are some situations in which not adjusting for baseline value rather than adjusting gives unbiased estimates. Generally, any spurious association between E and change ΔBP (ie, not resulting from a direct or indirect effect of E) needs to be controlled.

It is interesting to point out that all these recommendations depend on the causal relation between the exposure E and the baseline level of the outcome $BP(t_1)$.

Beyond adjusting for the baseline value of the outcome, it is worth considering the role of other relevant factors in the analysis. For example, Glymour et al[7] mentioned factors occurring before the beginning of the study which can influence the outcome $BP(t_1)$ at time t_1 as well as change of the outcome during the study. They showed how this "horse-racing effect" (using Peto's expression)[8] can bias the estimation of the effect of E on change when computing a linear regression adjusted for baseline level. Clarke[9] explicated a typical example in which age at the beginning of the study could be a causal factor for both the baseline value of the outcome and change from baseline. Under certain functional hypotheses, he suggested inclusion of $E \times age(t_1)$ interaction terms in models of change from baseline when estimating the causal effect of E on change.

All these elements are related to the underlying causal structure, which can be described explicitly by DAGs. Applying DAGs more systematically in studies of change from baseline could be useful in guiding the statistical analyses.

Our aim was to guide the choice of a statistical model (linear regression, adjusted or unadjusted for baseline outcome level) to estimate the causal effect of an exposure on change in outcome, using DAGs to represent a wide range of situations characterized by various study designs, regression-to-the-mean phenomena, and other relevant variables, such as pre-existing common factors (such as age) or additional confounders. We used graphical rules (like the d-separation rule) to interpret DAGs. These rules enable the analyst to identify potential biases when computing a model adjusted or unadjusted for the baseline blood pressure level. In general, estimating causal effects from variables measured with error can result in measurement bias. However, under additional structural and functional assumptions (no measurement error on the exposure E, outcomes following an approximately Gaussian distribution with a sufficiently large sample size and assuming a classic error measurement scheme as described below), path analysis principles can be applied in complement to DAG rules to show how the causal effect of interest between the exposure E and the latent change from baseline ΔBP could be estimated unbiasedly from the observed change from baseline ΔBP^* despite error on BP measurement.

Along with the graphical interpretation, we simulated data sets compatible with the causal structure of the DAGs and estimated the effect of the exposure on change applying both types of linear regression. Generation of the simulated data sets is described in the eAppendix; http://links.lww.com/EDE/A839, detailing the links between DAGs and algebra, and the links between models of change from baseline (ΔBP) and models of an outcome at a given time ($BP(t)$).

For simplicity, we will deal with a binary exposure ($E = 1$ for exposure vs. $E = 0$ for nonexposure). We focused on the situation of a complete and equal follow-up for every participant; in the case of variable follow-up, one would have to discuss additional hypotheses about independence of the length of follow-up with other variables in the system.

This article is organized according to the causal relation between the exposure E and the baseline level of the outcome $BP(t_1)$. The next section focuses on randomized studies. Next, we describe the case of nonrandomized studies with confounding factors influencing the exposure E, $BP(t_1)$ and ΔBP. Following that, we describe the case of nonrandomized studies in which the observed baseline value of blood pressure influences the exposure E ("cutoff designs"). Then, we describe nonrandomized studies where the exposure starts before the beginning of the study. Finally, discussion and concluding remarks are given.

We will use the following notations for two variables X and Y: β_X^Y is the path coefficient of $X \rightarrow Y$, σ_X^2 is the variance of X, and $\sigma_{X,Y}$ is the covariance between X and Y.

RANDOMIZED TRIALS

Figure 1A and B represents two causal structures corresponding to randomized trials. The exposure E is independent of the baseline blood pressure $BP(t_1)$ because of randomization. The outcome ΔBP is defined by the function $\Delta BP_i = BP_i(t_2) - BP_i(t_1)$. The manner in which the three variables $BP(t_1)$, $BP(t_2)$, and ΔBP could be represented in a DAG has been subject to debate.[10] Because of the deterministic nature of the relation among ΔBP, $BP(t_1)$, and $BP(t_2)$ whatever the level of the exposure E:

- $BP(t_2)$ and E are always conditionally independent given $BP(t_1)$ and ΔBP, and
- ΔBP and E are always conditionally independent given $BP(t_1)$ and $BP(t_2)$.

The "inductive causation algorithm" described by Pearl[11(ch. 2)] can be used as a tool to recover DAG structures from conditional independence relation. Pearl states that a pair of variables A and B cannot be connected by an edge if a set of variable S_{AB} can be found such that A and B are conditionally independent given S_{AB}. Consequently, we can neither draw any direct effect from E to $BP(t_2)$ nor from E to ΔBP in a DAG including all four variables: $BP(t_2)$ has to be deleted from a DAG showing E, $BP(t_1)$, and ΔBP to represent the causal effect of E on change ΔBP. It is possible to depict a causal structure showing E, $BP(t_1)$, and $BP(t_2)$ (without ΔBP), but such a DAG is not much help in encoding the relation between E and ΔBP. Examples of algebraic relation between the effect of E on ΔBP and the effect of E on $BP(t_2)$ are detailed in the eAppendix; http://links.lww.com/EDE/A839.

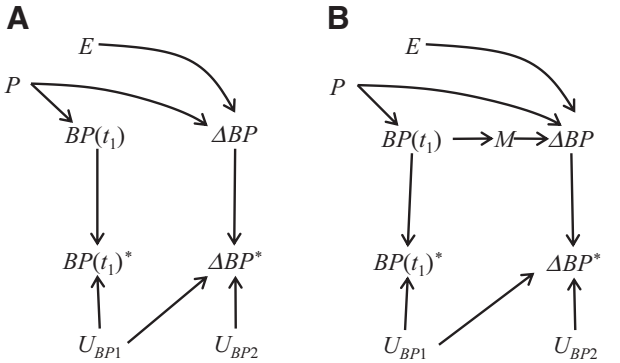

FIGURE 1. Causal structures corresponding to randomized trials. Regression to the mean is represented in each subfigure. U_{BP1} and U_{BP2} denote intra-individual variability and measurement error in blood pressure. P is a set of pre-existing variable with a causal influence on $BP(t_1)$ and ΔBP. Subfigure A represents the assumption that $BP(t_1)$ does not influence ΔBP. Subfigure B represents a causal influence of $BP(t_1)$ on ΔBP through an unmeasured intermediate variable M.

From the DAG of Figure 1A, one can discuss the possibility that $BP(t_1)$ influences ΔBP (such as through an intermediate and unmeasured mechanism represented by the variable M in Figure 1B).

In the DAGs in Figure 1, we added a set of pre-existing variables P with a causal influence on both $BP(t_1)$ and ΔBP. For example, the set P can include age at the beginning of the study ($age(t_1)$) which can be used to model the natural evolution of blood pressure with aging, as in the simulated examples (in this approach, we assume no cohort effects to simplify the model).

We used the notation $BP^*(t_1)$ and ΔBP^* for the observed blood pressure and change values, respectively.[12] The observed blood pressure is influenced by the unmeasured (latent) blood pressure $BP(t_1)$ and $BP(t_2)$ and intraindividual terms denoted U_{BP1} and U_{BP2} (which can include intraindividual variability and measurement error). We assume that $BP^*(t_1)$ and $BP^*(t_2)$ are defined according to a classic measurement error scheme in which

- $BP_i^*(t_1) = BP_i(t_1) + U_{BP1,i}$
- $BP_i^*(t_2) = BP_i(t_2) + U_{BP2,i}$
- U_{BP1} and U_{BP2} are independent exogenous variables from a Gaussian distribution of mean 0 and variance σ_U^2.

The observed change score is denoted ΔBP^* and is defined by $\Delta BP_i^* = \Delta BP_i + U_{PA2,i} - U_{PA1,i}$. From the assumptions regarding functional relation among $BP(t_1)$, $BP^*(t_1)$, ΔBP, and ΔBP^*, we have the following path coefficients values: $\beta_{BP(t_1)}^{BP^*(t_1)} = \beta_{U_{BP1}}^{BP^*(t_1)} = \beta_{\Delta BP}^{\Delta BP^*} = 1$ and $\beta_{U_{BP1}}^{\Delta BP^*} = -1$. Because we estimate the causal effect of the exposure on ΔBP from the observed variable ΔBP^*, the regression models become:

- adjusted for baseline level:

$$\Delta BP_i^* = \mu^* + \tau_{BP1}^* BP_i^*(t_1) + \tau_E^* E_i + \phi(E_i, P_i) + \varepsilon_i^* \qquad (3)$$

- unadjusted for baseline level:

$$\Delta BP_i^* = \mu^{*\prime} + \tau_E^{*\prime} E_i + \phi'(E_i, P_i) + \varepsilon_i^{*\prime} \qquad (4)$$

where the effect of the exposure on the observed change score is estimated by coefficients τ_E^* and $\tau_E^{*\prime}$ and where the functions ϕ and ϕ' can include interaction terms between E and $age(t_1)$ as in the simulated examples.

Graphical rules and conditions for interpreting DAGs and identifying causal effects are described elsewhere.[11,13] To facilitate the interpretation of the DAGs, readers can delete the arrow $E \rightarrow \Delta BP$ (showing the null hypothesis). Applying these graphical rules in causal structures of Figure 1, we can see that the causal effect of the exposure E on change ΔBP corresponds to the direct path $E \rightarrow \Delta BP$. As there is no unblocked back-door path between E and ΔBP, the potential expectation of ΔBP that would be observed if E was fixed to $E = e$, $\mathrm{E}(\Delta BP | \mathrm{do}(E = e))$ (using Pearl's notation) is identifiable; it can be estimated by $E(\Delta BP | E = e)$, indicating that the causal effect of E on ΔBP can be estimated by the coefficient $\tau_E{}'$ of the

linear regression unadjusted for $BP(t_1)$ (model 2).[11] The coefficient τ_E' cannot be estimated directly using model 2 because ΔBP is unobserved; however, by applying a path analysis we can easily show that $\tau_E^{*\prime} = \frac{\sigma_{E,\Delta BP^*}}{\sigma_E^2} = \frac{\sigma_{E,\Delta BP}}{\sigma_E^2} \times \beta_{\Delta BP}^{\Delta BP^*} = \tau_E'$, where $\tau_E^{*\prime}$ is estimated using model 4 with the observed change score ΔBP^*.[14] In addition, adjusting for $BP^*(t_1)$ does not activate any back-door path between E and ΔBP^*, and thus $\tau_E^{*\prime} = \tau_E^*$ and the causal effect of E on ΔBP could be estimated without bias by adjusting for $BP^*(t_1)$ in linear regressions (model 3) as well as without adjusting for $BP^*(t_1)$ (model 4).

The mean bias and standard error of the effect of E on ΔBP estimated from model 3 and model 4 applied on the simulated data are described in the Table. Both models gave unbiased estimations of the effect of E on ΔBP in causal structures of Figure 1, with smaller standard error using the linear regression adjusted for $BP^*(t_1)$. The greater power of this model was an expected result in randomized trials.[4] Vickers[15] showed that:

- power increases on an absolute scale for both models when the correlation between baseline and follow-up values is higher;
- with smaller correlations between baseline and follow-up values, baseline-adjusted models are comparably more efficient than the unadjusted models.

Nonrandomized Studies with Confounding Factors Between the Exposure and the Outcome

In Figure 2A and B, the two initial causal structures have an additional baseline confounder (or a set of confounders) C that influences the exposure E as well as $BP(t_1)$ and ΔBP. As in the previous section, pre-existing variables P (such as age at the beginning of the study) can influence $BP(t_1)$ and ΔBP. Interestingly, when confounders C have the same effect on $BP(t_1)$ as on $BP(t_2)$, they do not affect change over time in blood pressure so that Figure 2A and B can be simplified into the structures of Figure 2C and D. One could consider these causal structures under some additional functional assumptions such as no modification of the effect of C on $BP(t)$ over time. Because the situation of common causes of E and $BP(t)$ does not equate to common causes of E and ΔBP, simplifying the causal structure might not appear straightforward.

When All Baseline Confounders *C* Are Measured

In such a situation, we can block all back-door paths between E and ΔBP^*. The causal effect of E on ΔBP^* is thus identifiable and we can estimate without bias the effect of E on ΔBP using linear regression analyses adjusted for the confounders C, whether or not $BP^*(t_1)$ is adjusted for. Assuming no effect modification by C, we would use the following models:

– adjusted for baseline level:

$$\Delta BP_i^* = \mu^* + \tau_{BP1}^* BP_i^*(t_1) + \tau_E^* E_i + \tau_C^* C_i + \phi^*(E_i, P_i) + \varepsilon_i^* \quad (5)$$

– unadjusted for baseline level:

$$\Delta BP_i^* = \mu^{*\prime} + \tau_E^{*\prime} E_i + \tau_C^{*\prime} C_i + \phi^{*\prime}(E_i, P_i) + \varepsilon_i^{*\prime} \quad (6)$$

When Some Baseline Confounders *C* are Unmeasured

In this case, the estimation of the causal effect of the exposure E on ΔBP is expected to be biased, with the

TABLE. Mean Bias and Standard Error (in mmHg) of the Estimation of the Effect of the Exposure *E* on Blood Pressure Change (ΔBP), Using Linear Regressions Adjusted for $BP^*(t_1)$ (Model 3) or Unadjusted for $BP^*(t_1)$ (Model 4), in Simulated Data Sets Compatible with the Causal Structures Represented in Figures 1–4

Figures	Regression Model	Graph Interpretation	Mean Bias	SE	Graph Interpretation	Mean Bias	SE	Graph Interpretation	Mean Bias	SE
Figure 1		Subfigure A			Subfigure B					
Randomized study	Adjusted for $BP^*(t_1)$	Unbiased	0.06	1.42	Unbiased	0.04	1.35	—	—	—
	Unadjusted for $BP^*(t_1)$	Unbiased	0.06	1.50	Unbiased	0.05	1.42	—	—	—
Figure 2		Subfigure A			Subfigure C			Subfigure D		
Nonrandomized study with unmeasured confounder *C*	Adjusted for $BP^*(t_1)$	Biased	1.24	1.81	Biased	0.77	1.62	Biased	1.04	1.75
	Unadjusted for $BP^*(t_1)$	Biased	0.93	1.56	Unbiased	−0.05	1.66	Biased	0.58	1.69
Figure 3		Subfigure A			Subfigure B			Subfigure C		
Nonrandomized study $BP^*(t_1)$ influences *E*	Adjusted for $BP^*(t_1)$	Unbiased	0.19	1.99	Unbiased	0.18	1.95	Biased	1.17	1.65
	Unadjusted for $BP^*(t_1)$	Biased	−1.64	1.41	Biased	−1.46	1.57	Biased	0.40	1.48
Figure 4		Subfigure A			Subfigure B					
Nonrandomized study *E* influences both $BP(t_1)$ and ΔBP	Adjusted for $BP^*(t_1)$	Biased	−8.75	4.08	Biased	−6.86	5.76	—	—	—
	Unadjusted for $BP^*(t_1)$	Unbiased	0.00	0.75	Unbiased	0.05	0.85	—	—	—

In each scenario, 1050 samples of size 500 have been simulated according to the causal structures represented in Figures 1–4.
SE indicates standard error of the estimated effect of *E* on ΔBP.

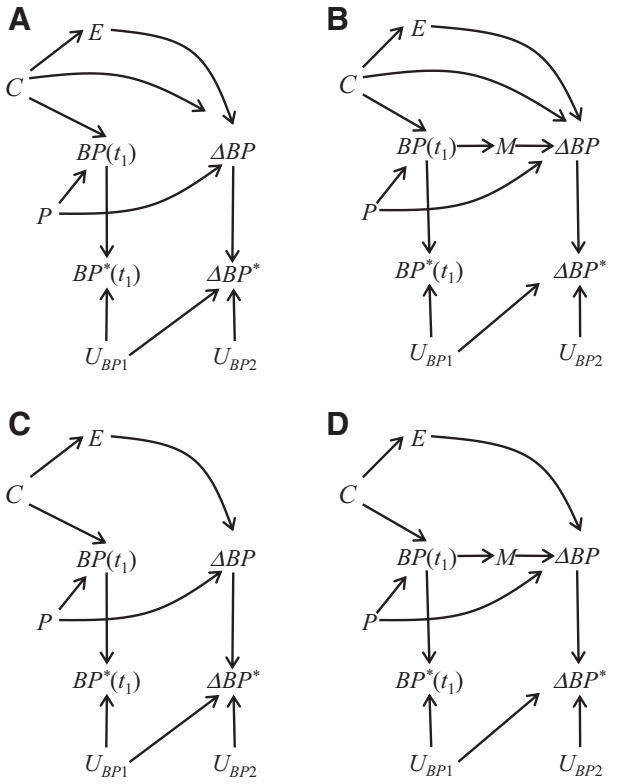

FIGURE 2. Causal structures with confounders *C* between the exposure *E* and change *ΔBP*. Subfigures A and C represent the assumption that $BP(t_1)$ does not influence *ΔBP*. Subfigures B and D represent a causal influence of $BP(t_1)$ on *ΔBP* through an unmeasured intermediate variable *M*. Subfigures C and D represent the assumption that confounder C does not influence *ΔBP* (except through the exposure *E*).

notable exception of applying a regression unadjusted for $BP^*(t_1)$ in Figure 2C:

(i) Applying a linear regression adjusted for $BP^*(t_1)$ but unadjusted for some unmeasured confounders *C* (model 3), the estimation of the effect of *E* on *ΔBP* by τ_E^* is expected to be biased due to the following back-door paths in all structures of Figure 2:
- the back-door path resulting from adjusting for the collider $BP^*(t_1)$, which creates a spurious correlation between $BP(t_1)$ and U_{PA1}: $E \leftarrow C \rightarrow BP(t_1)$ - - - $U_{PA1} \rightarrow \Delta BP^*$;
- two potential back-door paths that cannot be blocked if *C* and *M* are unmeasured: $E \leftarrow C \rightarrow \Delta BP \rightarrow \Delta BP^*$ in Figure 2A and B, and $E \leftarrow C \rightarrow BP(t_1) \rightarrow M \rightarrow \Delta BP \rightarrow \Delta BP^*$ in Figure 2B and D.

(ii) Applying a linear regression model unadjusted for $BP^*(t_1)$ (model 4), the estimation of the effect of *E* on *ΔBP* by $\tau_E^{*\prime}$ is expected to be biased because of the following back-door paths in Figure 2A, B, and D where *C* and *M* are unmeasured:
- the unblocked back-door path $E \leftarrow C \rightarrow \Delta BP \rightarrow \Delta BP^*$ (Figure 2A and B);
- the unblocked back-door path $E \leftarrow C \rightarrow BP(t_1) \rightarrow M \rightarrow \Delta BP \rightarrow \Delta BP^*$ (Figure 2B and D).

(iii) However, in the causal structure depicted in Figure 2C, there are only two back-door paths between *E* and ΔBP^*: $E \leftarrow C \rightarrow BP(t_1) \rightarrow BP^*(t_1) \leftarrow U_{BP1} \rightarrow \Delta BP^*$ and $E \leftarrow C \rightarrow BP(t_1) \leftarrow P \rightarrow \Delta BP \rightarrow \Delta BP^*$. These back-door paths are blocked when one does not condition on $BP^*(t_1)$ so that the causal effect of *E* on *ΔBP* could be estimated unbiasedly by the coefficient $\tau_E^{*\prime} = \frac{\sigma_{E,\Delta BP}}{\sigma_E^2} \times \beta_{\Delta BP}^{\Delta BP^*} = \tau_E'$ applying an unadjusted regression for the baseline value of the outcome (model 4), despite the unmeasured set of variables *C*.

In the Table, we show illustrative results from simulated data sets compatible with the causal assumptions in Figure 2, where *C* is a binary unmeasured confounder with no modification of the effect of *E* by *C*, and where the direct effect of $C \rightarrow BP(t)$ is either modified by $age(t_1)$ (Figure 2A) or unmodified by $age(t_1)$ (Figure 2C and D). These results are consistent with the above graphical interpretation completed by path analysis. We did not simulate data from Figure 2B as they would not provide additional information to the simulations from Figure 2A and D.

Nonrandomized Studies in Which the Observed Baseline Outcome Influences the Exposure

In Figure 3A and B, we add a causal influence from the observed blood pressure $BP^*(t_1)$ to the exposure *E* in the causal structures of Figure 1. For example, an antihypertensive treatment may be more frequently given to patients with higher observed blood pressure at the beginning of the study. Such a causal structure also corresponds to the cutoff design mentioned by Senn.[1]

The estimate of the causal effect of *E* on *ΔBP* is expected to be biased using a linear regression unadjusted for $BP^*(t_1)$ (model 4), because the association between *E* and ΔBP^* estimated by the coefficient $\tau_E^{*\prime}$ corresponds to the indirect path of interest $E \rightarrow \Delta BP \rightarrow \Delta BP^*$ and one or two unblocked back-door paths:

– $E \leftarrow BP^*(t_1) \leftarrow U_{BP1} \rightarrow \Delta BP^*$ in Figure 3A and B;

– $E \leftarrow BP^*(t_1) \leftarrow BP(t_1) \rightarrow M \rightarrow \Delta BP \rightarrow \Delta BP^*$ in Figure 3B.

Another back-door path is present in Figure 3A and B, $E \leftarrow BP^*(t_1) \leftarrow BP(t_1) \leftarrow P \rightarrow \Delta BP \rightarrow \Delta BP^*$, but it can be blocked by adjusting for *P*.

In using the linear regression analysis adjusted for baseline level (model 3), the adjustment for $BP^*(t_1)$ blocks all these back-door paths and the estimated coefficient τ_E^* is only explained by the indirect path $E \rightarrow \Delta BP \rightarrow \Delta BP^*$. The causal effect of *E* on *ΔBP* could be estimated without bias by the coefficient τ_E^*, as we can see by applying the following path analysis:

$$\tau_E^* = \frac{\sigma_{E,\Delta BP^*}}{\sigma_E^2} = \frac{\sigma_{E,\Delta BP}}{\sigma_E^2} \times \beta_{\Delta BP}^{\Delta BP^*} = \frac{\sigma_{E,\Delta BP}}{\sigma_E^2}.$$

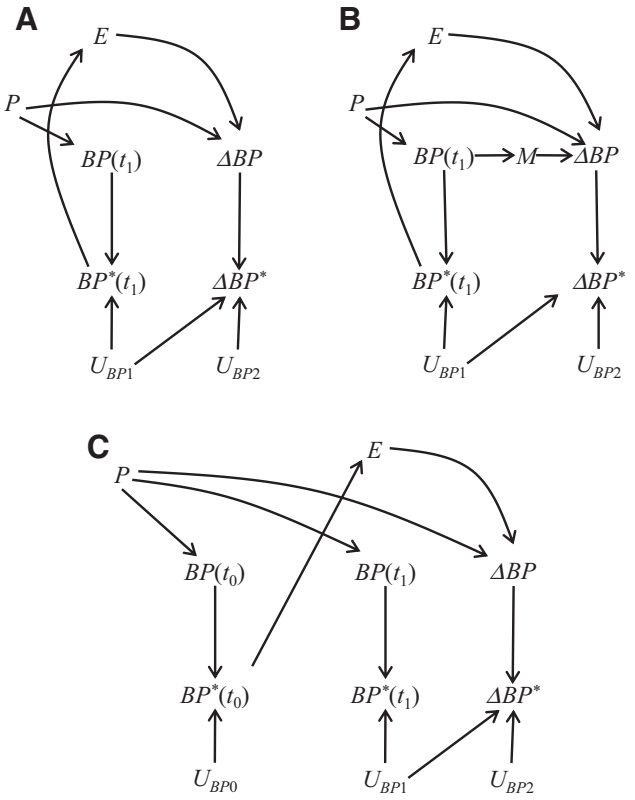

FIGURE 3. Causal structures in which the observed outcome at the beginning $BP(t_1)^*$, or before the beginning of the study $BP(t_0)^*$, influences the exposure *E*. Subfigures A and C represent the assumption that $BP(t_1)$ does not influence ΔBP. Subfigure B represents a causal influence of $BP(t_1)$ on ΔBP through an unmeasured intermediate variable *M*.

Consistent results from simulated data sets compatible with the causal assumptions in Figure 3A and B are presented in the Table.

This situation could be extended to a causal structure in which pre-existing measured values of the "outcome" variable confounds the relation between *E* and change from baseline. A simple example is given in Figure 3C, where $BP(t_0)$ is a pre-existing value of blood pressure, $BP^*(t_0)$ rather than $BP^*(t_1)$ influences *E*, and the set of pre-existing variables *P* could include an age variable $age(t_0)$. These variables $BP^*(t_0)$ and *P* are not usually collected and are therefore unavailable for analysis. In this DAG, the back-door path $E \leftarrow BP^*(t_0) \leftarrow BP(t_0) \leftarrow P \rightarrow \Delta BP \rightarrow \Delta BP^*$ connects *E* to ΔBP^*. If $BP^*(t_0)$ and *P* are unmeasured, it cannot be blocked by adjusting for $BP^*(t_1)$, resulting in a bias when estimating the causal effect of *E* on ΔBP^* using model 3. In the simulated data set derived from Figure 3C, we can see that computing models 3 or 4 gave biased estimations of the causal effect of *E* on ΔBP (Table). In the example of Figure 3C, one could adjust for $BP^*(t_0)$ to get an unbiased estimation of the causal effect of *E* on ΔBP. In a more general way, it can be useful to characterize the pre-existing evolution of the "outcome" variable.[16]

A final point on cutoff designs is that the positivity assumption should be examined carefully. This assumption is needed to identify causal effects; it holds when the probability of being exposed to every level of exposure is greater than zero for every combination of the values of the confounders in the population.[17] For example, there is a clear positivity violation in a cutoff design where all subjects with $BP^*(t_1) <$ 150 mmHg are unexposed to *E* and all subjects with $BP^*(t_1) \geq$ 150 mmHg are exposed to *E*. The positivity violation can be examined using propensity scores or by a descriptive tabular analysis of the exposure according to combinations of confounder values.[17]

Nonrandomized Studies in Which the Exposure Starts Before the Beginning of the Study

In Figure 4, the causal structures differ from the previous ones by an exposure that starts before the beginning of the study and influences both $BP(t_1)$ and ΔBP, as in the examples given by Lord and Glymour et al.[3,7]

In the causal structures of Figure 4, there is no unblocked back-door path between the exposure *E* and the observed change score ΔBP^*. The effect of *E* on ΔBP is explained by one or two paths, resulting in a causal effect equal to $\frac{\sigma_{E,\Delta BP}}{\sigma_E^2}$:

- $E \rightarrow \Delta BP$ in Figure 4A and B;
- and $E \rightarrow BP(t_1) \rightarrow M \rightarrow \Delta BP$ in Figure 4B.

This effect could be estimated without bias by the coefficient $\tau_E^{*\prime}$ using a linear regression unadjusted for $BP^*(t_1)$ (model 4):

$$\tau_E^{*\prime} = \frac{\sigma_{E,\Delta BP}}{\sigma_E^2} \times \beta_{\Delta BP}^{\Delta BP^*} = \frac{\sigma_{E,\Delta BP}}{\sigma_E^2}.$$

Using the linear regression analysis adjusted for $BP^*(t_1)$ (model 3), a spurious correlation between $BP(t_1)$ and U_{BP1} is created and adds a back-door path between *E* and ΔBP^*: $E \rightarrow BP(t_1)$ - - - $U_{BP1} \rightarrow \Delta BP^*$. This back-door path biases the estimation of the causal effect of *E* on ΔBP, as it is included in the association estimated by the coefficient τ_E^* of model 3.

Results from the simulated data sets were consistent with the graphical interpretation (Table).

DISCUSSION

The approach, based on DAGs with some functional hypotheses to carry out path analyses, confirms the lack of bias in randomized studies, whatever the chosen model. It clarifies why adjusting for the observed baseline outcome value can be recommended in many studies in which the baseline outcome influences the exposure (Figure 3). The particularities of the causal structures in Figure 3 (including cutoff designs) may not have been widely highlighted in the epidemiologic literature. They are contrasted with structures of Figure 4 (where the exposure starts before the beginning of the study), in which using linear regression unadjusted for the baseline value appears to be the best choice. Finally, the approach points out

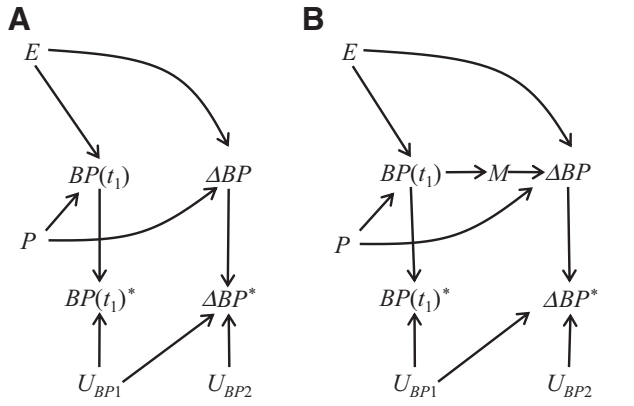

FIGURE 4. Causal structures in which the exposure *E* starts before the beginning of the study. Subfigure A represents the assumption that $BP(t_1)$ does not influence ΔBP. Subfigure B represents a causal influence of $BP(t_1)$ on ΔBP through an unmeasured intermediate variable *M*.

critical assumptions to be discussed when some variables confound the exposure–outcome relation (Figure 2).

In our view, randomization, confounding through a third variable (*C*) or the observed outcome $BP^*(t_1)$ at the beginning of the study, start of the exposure, natural evolution of the outcome in time, and intraindividual variability are the main points to discuss. Of course, all of the possible causal structures cannot be reduced to the few situations described above. In particular, more complex combinations implying confounders between the exposure and the outcome (as in Figure 2) were not described above:

(i) Confounding between the exposure *E* and change ΔBP through confounders *C* and through the observed $BP^*(t_1)$ (combining Figures 2 and 3). In such a case, one has to adjust for the baseline outcome level, as well as for the set of confounders *C*. Bias is most likely inevitable if *C* contains unmeasured variables that cannot be adjusted for.

(ii) An early exposure *E* before the beginning of the study, and confounding between *E* and change ΔBP through variables *C* (combining Figures 2 and 4). In such a case, one has to apply a linear regression model unadjusted for the baseline outcome level, but adjusted for variables *C*. Combining Figures 2C and 4A, under the assumption of no effect modification of *C* on blood pressure over time, a linear regression analysis unadjusted for $BP^*(t_1)$ could still give an unbiased estimation even if some variables in *C* are unmeasured.

Many of the causal assumptions represented in Figures 1–4 rely on the analyst's judgment rather than on observed data.

- The assumption that there are no unmeasured confounders *C* in Figure 2 is typically untestable.
- More complex measurement errors can be represented in DAGs and should be discussed. For example, one might draw a direct causal influence from $BP(t_1)$ to U_{BP1} to take into account ceiling or floor effects.[7] One could consider some dependent (with a common parent of U_{BP1} and U_{BP2}) or differential measurement error (with a causal effect of *E* on U_{BP1} or U_{BP2}).[12] These measurement errors could add some bias according to the underlying causal structure and the applied estimation method.
- A challenging assumption concerns the potential influence of $BP(t_1) \rightarrow \Delta BP$. Such an assumption will usually be drawn from pathophysiologic knowledge. Furthermore, one could consider that a nonlinear functional model would be more appropriate to model BP change in that case.

Another recurrent question relates to the effect modification of *E* on change ΔBP by the baseline outcome $BP(t_1)$ (or, more pragmatically, by the observed value $BP^*(t_1)$). Following the classification provided by VanderWeele et al,[18] $BP^*(t_1)$ could be an effect modifier by proxy or by common cause in Figures 1–3 on ΔBP. In these situations, effect modification by $BP^*(t_1)$ can be estimated by applying a linear regression adjusted for $BP^*(t_1)$ and appropriately adjusted for the confounders *C* and pre-existing variables *P*. $BP(t_1)$ or $BP^*(t_1)$ cannot be an effect modifier in the causal structures of Figure 4 because they are descendants of the exposure *E* (Theorem 1 in VanderWeele et al[18]).

Although our paper has focused on linear regressions, the causal structures depicted in Figures 1–4 could also be used to consider adjusting for $BP^*(t_1)$ in a logistic regression or a time-to-event model when the outcome is defined from ΔBP (eg, $Y = 1$ if $\Delta BP < -5$ mmHg, $Y = 0$ otherwise). However, because these are nonlinear models, path analysis principles should not be applied, and the estimated causal effect could still be distorted due to measurement error. Analyses of change from baseline are complex, and using DAGs turns out to be a very useful approach to choosing the most appropriate linear model. As these tools rely on partly untestable assumptions (such as unmeasured confounding), the analyst should attempt to gather meaningful arguments to discuss them. Among other approaches, one can test some independence or conditional independence relation to check whether the observed data are compatible with the assumptions depicted in the DAG. Intraindividual variability and measurement error could be explored through reviews of the literature or repeated measures of the outcome at a given time in a subsample of the study population. In some cases, corrective methods can be implemented.[7] Plots of the outcome against age can give indications of the general shape of the outcome evolution and guide the choice of a functional relation between the exposure and the change score. Several alternative causal structures can be examined to look for potential biases and carry out sensitivity analyses.

ACKNOWLEDGMENTS

We thank Nina Crowte, Mary Iagnemma, and Michelle Kelly-Irving for correcting English grammar and spelling.

REFERENCES

1. Senn S. Change from baseline and analysis of covariance revisited. *Stat Med*. 2006;25:4334–4344.
2. Laird N. Further comparative analyses of pretest-posttest research designs. *Am Stat*. 1983;37:329–330.
3. Lord FM. A paradox in the interpretation of group comparisons. *Psychol Bull*. 1967;68:304–305.
4. Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. *J Clin Epidemiol*. 2006;59:920–925.
5. Bland JM, Altman DG. Regression towards the mean. *BMJ*. 1994;308:1499.
6. Bland JM, Altman DG. Some examples of regression towards the mean. *BMJ*. 1994;309:780.
7. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. *Am J Epidemiol*. 2005;162:267–278.
8. Peto R. The horse-racing effect. *Lancet*. 1981;2:467–468.
9. Clarke PS. Causal analysis of individual change using the difference score. *Epidemiology*. 2004;15:414–421.
10. Shahar E, Shahar DJ. Causal diagrams and change variables. *J Eval Clin Pract*. 2012;18:143–148.
11. Pearl J. *Causality: Models, Reasoning, and Inference*. 2nd ed. New York: Cambridge University Press; 2009.
12. Hernán MA, Cole SR. Invited commentary: causal diagrams and measurement bias. *Am J Epidemiol*. 2009;170:959–962.
13. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10:37–48.
14. Loehlin JC. *Latent Variable Models: An Introduction to Factor, Path, and Structural Equation Analysis*. 4th ed. Mahwah, NJ: L. Erlbaum Associates; 2004.
15. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Med Res Methodol*. 2001;1:6.
16. Haviland A, Nagin DS, Rosenbaum PR, Tremblay RE. Combining group-based trajectory modeling and propensity score matching for causal inferences in nonexperimental longitudinal data. *Dev Psychol*. 2008;44:422–436.
17. Westreich D, Cole SR. Invited commentary: positivity in practice. *Am J Epidemiol*. 2010;171:674–677.
18. VanderWeele TJ, Robins JM. Four types of effect modification: a classification based on directed acyclic graphs. *Epidemiology*. 2007;18:561–568.