Twin Research (2000) 3, 159–164
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Defining discordance in twin studies of risk and protective factors for late life disorders

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In studies that employ matched pair analysis to identify environmental exposures important for a disorder, criteria for discordant pairs are seldom discussed. Yet several assumptions concerning the definition of discordancy may have considerable influence over what results are found. Problems are exacerbated when age of onset for a disorder is late in life. We propose a new set of criteria for defining discordant pairs in studies of dementia, taking into account duration of discordance and competing causes of mortality, and evaluate the consequences of choosing alternative definitions of discordancy. Twin Research (2000) 3, 159–164.

Keywords: co-twin control, Alzheimer's disease, dementia, genetic epidemiology

Introduction

Discordance is a critical concept in twin studies of risk and protective factors for disease. Epidemiologists employ an approach variously called co-twin control or matched pair design. This design capitalizes on pairs who are both discordant for the disease and discordant for an exposure of interest. The number of sick twins with the exposure whose partner is healthy and unexposed is compared with the number of sick twins without the exposure whose partner is healthy and has the exposure. A McNemar test[1] is used to estimate statistical significance. Very little attention appears to have been paid to defining discordance. Most reports about discordant twin pairs simply state that discordant pairs were used, presuming that it is obvious that one twin has the disorder and the other twin does not. The purpose of this paper is to draw attention to some of the problems that arise in genetic epidemiological studies of late onset age-related disorders, such as dementia, and to suggest an approach to defining discordancy.

Dementia has become recognized as a major public health problem in older adults. The most common dementing disorder is Alzheimer's disease, which involves gradual decline in multiple cognitive domains, especially memory, with the decrement sufficient to interfere with usual activities and social functioning. Across different countries, incidence and prevalence figures for dementia increase nearly exponentially with age. Prevalence studies converge on rates of approximately 0.5 cases per 100 people in the age group 60 to 65 years, increasing to 12 cases per 100 people in the age group 80 to 85 years.[2] There is some uncertainty whether or not there is a plateau after 90 to 95 years of age.[3]

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Received 23 March 2000; revised 22 May 2000; accepted 6 June 2000

Concordance

Considerable attention has been paid by twin researchers to defining concordance. Concordance rates are a measure of resemblance for qualitative traits such as diseases or disorders. Concerns include the procedures by which twin pairs are ascertained from a population, such that biases are avoided,[4,5] as well as methods of calculating concordance rates.[6,7] For disorders such as schizophrenia, different diagnostic criteria have been found to show different results, and concordances may be computed based on either a constrained definition of disorder or a spectrum diagnosis, eg schizotypy.[8]

Writers about concordance have been concerned about age of onset and age-related risk for disorder. For example, in studying schizophrenia, Gottesman and Shields[9] discussed the fact that co-twins should be followed beyond the period of risk for first occurrence of a disease episode. Pickles et al[10] dealt with age-relatedness by developing models for looking at concordance for age of onset, in this case, for puberty.

Age of onset has been recognized as a particular problem in the study of disorders associated with aging, such as dementia. When a disease has late onset, relatives may be studied before the age at

https://doi.org/10.1375/twin.3.3.159 Published online by Cambridge University Press

which they would manifest the disease, or they may die of other causes before having the opportunity to manifest the disease.[8] Unlike menarche or even a disorder such as schizophrenia, where a time can be specified after which onset is unlikely, risk for dementia continues to increase, at least to age 90 or 95.[3] Concordance for disorder becomes confounded with concordance for survival. Effects of censoring can be considerable.

Discordance

Issues of diagnosis, age of onset, and duration of discordance have profound implications for defining discordance as well as concordance. Late-onset age means that many pairs will not be informative for matched pair designs because the partner will have died before the age at which the proband developed the disorder. Even if both are alive at the first twin's age of onset for dementia, there is still a question as to when a pair should be considered discordant. Imagine a population of twins that is screened for all existing cases of a disorder. Consider a hypothetical pair (shown in Figure 1) where only one has dementia, but this twin has an age of onset 2 years before the study. Consider another pair, where both are demented, but the first twin became demented 10 years ago and the co-twin only 1 year before the study. All are alive when the study begins. Should the former pair be counted as discordant, while the latter is considered concordant? In addition, implicit in calling a pair discordant is that they are sufficiently different to represent different etiological processes. For example, if a monozygotic twin pair has remained discordant for dementia for 9 years, the role of environmental factors would seem to be implicated, and the pair is informative for matched pairs analysis. Indeed, in some of the original literature about using the Swedish Twin Registry to study risk factors, Medlund et al[11] mention that pairs who both have a disease can be used in co-twin control analyses if there is information about onset of the illness. However, they do not expand on this point or suggest which pairs to use.

Although their concern was not discordant pairs, Meyer and Breitner[12] tried to avoid the problem posed here by extending the approach developed by Pickles et al[10] to Alzheimer's disease, placing pairs into contingency tables where the size of the table was a function of the last age of observation or death. These models typically use some sort of arbitrary age bands (often 5 years long) to define thresholds. Thus, a pair when one is affected one year earlier than the co-twin could end up in a different age band and would contribute equally to discordance for age of onset as a pair with an intrapair difference of 9 years. Even in these models, duration of discordance is a hidden issue.

A further difficulty can stem from accuracy of establishing age of onset. Alzheimer's disease is by definition a disease with insidious onset. This is one of the diagnostic criteria. Particularly if a person has been demented for some time, and depending on the quality of the informant, the age of onset will only be approximate. Even with excellent information, determining exactly the point at which the criteria for diagnosing dementia are met is not easy, as cognitive changes may precede the dementia by a number of years, and determining when the impairment sufficiently interferes with daily functioning is not clear cut.

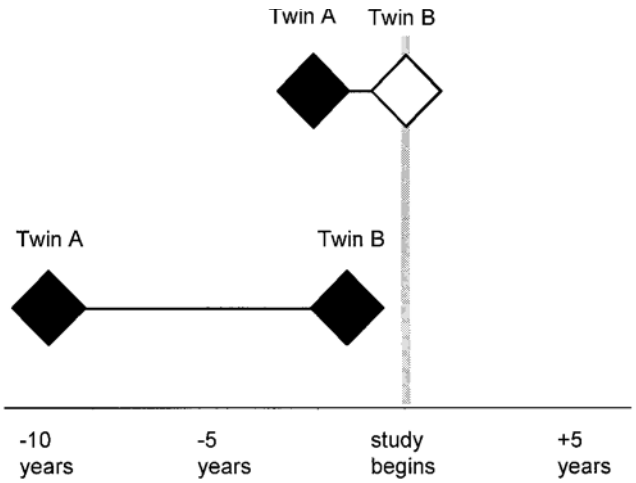

Figure 1 Hypothetical example of twin pairs, illustrating dilemmas in defining discordance. Solid diamonds represent demented twins; open diamonds represent cognitively intact twins

Current practice

Several examples of matched pair designs can be found for studies of dementia as well as other late life disorders. In a study of twin pairs discordant for Parkinson's disease, Bharucha et al[13] required only that both members of the twin pair be alive. Pairs were classified as discordant if one was diagnosed with the disorder, whereas the other was not. Similarly, in a study of osteoarthritis with the Finnish twin cohort,[14] if one member of the pair indicated having been told that he or she had osteoarthritis and the other member of the pair said no, the pair was used in an analysis of risk factors. The age of the sample of discordant pairs was 33 to 54, meaning that some of these pairs would almost certainly become concordant, and their intrapair interval might well be less than the intrapair interval of concordant pairs included in the study. Likewise,

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in an analysis of twin pairs from the Finnish twin cohort who were discordant for Alzheimer's disease, Raiha et al[15] included pairs as discordant if one member of the pair had a diagnosis of Alzheimer's disease and the other did not. There was no indication of how long after the proband's onset the partner was followed. Partners could hypothetically become demented within a year of the proband's onset and still be counted as discordant. Nee and Lippa[16] conducted a 13-year follow up of a volunteer sample of 22 twin pairs where one or both had Alzheimer's disease. Ten pairs remained discordant. Number of concordant pairs increased from 9 at baseline to 12 at follow up. Among the concordant pairs, average intrapair difference in age of onset was 6.4 years, with a range of 0 to 16 years. These authors looked at risk factors both in pairs who remained discordant and pairs who differed in age of onset.

In one of the few examples of operationalizing discordancy for purposes of co-twin control analyses, Breitner et al[17] used the rule (graphically portrayed in Figure 2) that a pair who have subsequently become concordant must have remained discordant for over 3 years in order to be considered discordant (top row of figure), or the partner must be alive and intact over 3 years after the proband's age of onset (middle row), or the partner must have lived over 3 years past the proband's age of onset and died intact (bottom row). These criteria represent a step forward. At the same time, there are reasons to question the choice of 3 years, including difficulties in pinpointing age of onset, and how many years is sufficient to assure that different etiological processes are suggested in the co-twins.

Posner et al[18] carried out a lifetable analysis looking at time to onset of dementia in initially unaffected twins from when their partner was diagnosed with Alzheimer's disease. After 3 years, the probability of the co-twin being cognitively intact and hence the pair still discordant remained 93%. By 6 years, the probability had decreased to 79%, and after 10 years, to 71%; and after 16 years, to 34%. These results indicate that the probability of becoming demented 3 years or less after the proband becomes demented is relatively low, yet a good number of these pairs do become concordant in the next several years.

Criteria for discordant pairs

We propose a new set of criteria for use in identifying discordant twin pairs for a matched pair designing studying risk or protective factors for a late onset disorder. These are illustrated in Figure 3. There are three groups of interest:

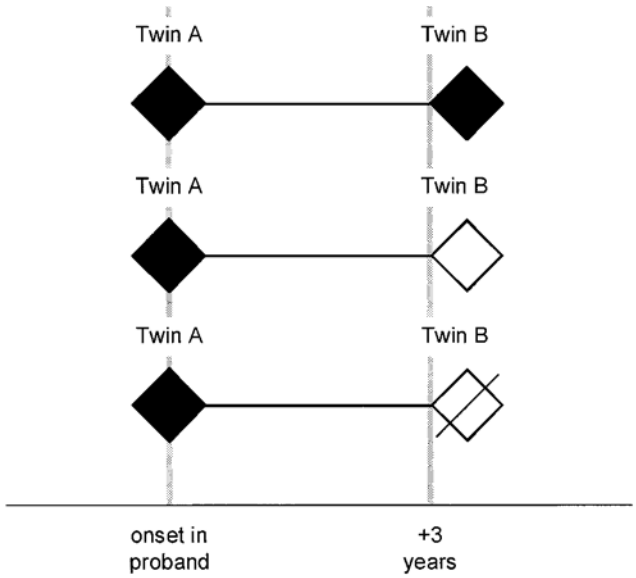

Figure 2 Portrayal of three year rule for defining discordant twin pairs, following Breitner et al,[17] showing three types of pairs that would be regarded as discordant under the rule. Solid diamonds represent demented twins; open diamonds represent cognitively intact twins; open diamonds with a slash represent twins who died and were cognitively intact

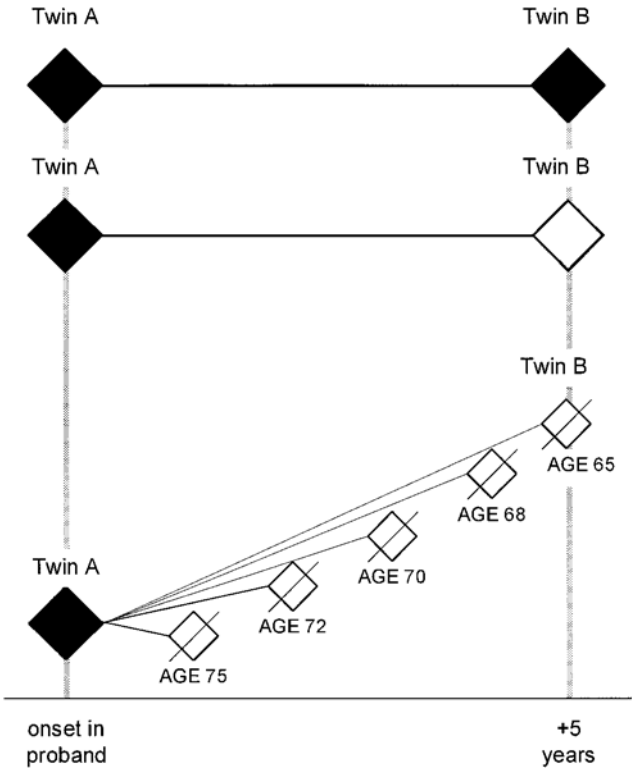

Figure 3 Portrayal of proposed criteria for defining discordant twin pairs for matched pairs analyses of dementia. Age 65 etc refers to age of onset in the affected twin

https://doi.org/10.1375/twin.3.3.159 Published online by Cambridge University Press

(1) pairs who are now concordant but who were discordant for some period of time;

(2) pairs in which one member of the pair is demented and the other member has been clinically evaluated and continues to be non-demented;

(3) pairs in which one member of the pair is demented and the other member of the pair has died.

With respect to the first group, who eventually become concordant, in order to call this pair discordant we propose a 5-year difference between age of onset of the first twin and age of onset of the partner. This 5-year period reflects the interval suggested by the survival curve in Posner et al.[18] In addition, 5 years provides a margin of error around age of onset. By extension, for the second group, we must also require a 5-year interval during which an alive, intact partner is followed to assure that he or she does not develop dementia.

For the third group, it would also be possible to require that the partner stay living for at least 5 years after the proband's age of onset. However, with increasing age, there are more competing causes of mortality. It is a strong requirement for twins who become demented at age 85 to have their co-twins survive to age 90. Therefore, we propose a sliding scale for how long a co-twin must remain alive, before dying intact. For twins who became demented at age 65 or younger, 5 years are required. At the other end of the scale, for twins who became demented after age 75, we simply require that the partner remain alive past the proband's age of onset and be established to have been cognitively intact at the time of death.

We applied these three alternative rules to data from the Study of Dementia in Swedish Twins,[19] using 90 pairs who were both alive at the proband's age of onset, and where we have followed pairs longitudinally. Table 1 compares (a) no rule beyond requiring that both members of the pair be alive, which is the rule implicit in most literature, (b) the Breitner et al[17] 3-year rule, and (c) the proposed sliding 5-year rule. With no rule, five pairs who were discordant when first ascertained have since become concordant, and intrapair difference in age of onset for concordant pairs is quite large – nearly as great as the duration of follow up in the pairs who have not become concordant. With the 3-year rule, a number of pairs who become concordant between 3 and 5 years after the proband's age of onset are included with the discordant pairs, and a substantial number of pairs cannot be used because the cognitively intact partner did not survive for 3 years after the proband's age of onset, due to other causes of mortality. The sliding 5-year rule is more lenient about pairs where the cognitively intact partner dies for other reasons, but is the most strict with respect to intrapair difference in age of onset in order to be considered discordant.

Consequences of applying alternative criteria

Table 2 shows results from evaluating a simulated neurotoxic exposure. Column 1 shows the results under the implicit rule. For purposes of this table, two other columns were added, starting with the data for the 'no rule' group. In the first additional

Table 1 Comparison of criteria for defining discordancy

	No rule	3-year rule	Sliding 5-year rule
concordant pairs intrapair difference in age of onset	N=26 (13 MZ, 13 DZ) mean=6.38 (SD=4.96), range=0 to 16.5 years	N=11 (3 MZ, 8 DZ) mean=1.68 (SD=1.15), range=0 to 3 years	N=17 (7 MZ, 10 DZ) mean=2.56 (SD=1.54), range=0 to 4.5 years
discordant pairs intrapair difference in age of onset for pairs who eventually became concordant	N=57 (17 MZ, 40 DZ) n=5 pairs, mean=8.00 (SD=3.39), range=3 to 11 years	N=63 (23 MZ, 40 DZ) n=23 pairs, mean=8.41 (SD=4.17), range=3.5 to 16.5 years	N=66 (22 MZ, 44 DZ) n=17 pairs, mean=9.91 (SD=3.82), range=5 to 16.5 years
duration of follow up of intact partner in pairs who remained discordant	n=52 pairs, mean=7.48 (SD=5.41), range=0.5 to 23 years	n=40 pairs, mean=9.19 (SD=5.03), range=4 to 23 years	n=49 pairs, mean=7.78 (SD=5.45), range=0.5 to 23 years
pairs excluded by the rule	N/A	7 pairs: not yet sufficient duration of follow up with living intact partner. 9 pairs: partner did not live 3 or more years after the proband's age of onset	7 pairs: not yet sufficient duration of follow up with living intact partner

'no rule'=both members of pair are alive at proband's onset, no longitudinal follow up. '3 year rule'=pairs remain discordant for over 3 years (see Figure 2). 'sliding 5-year rule'=pairs remain discordant for 5 years, with sliding interval in case of death of partner after proband's onset (see Figure 3).

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Table 2 Consequences of alternative criteria for defining discordancy

Individuals with dementia exposed, %	Individuals without dementia exposed, %	Column 1: 'no rule' Odds ratio (95% CI)	Column 2: no rule, with 3× greater misclassification revealed upon longitudinal follow up Odds ratio (95% CI)	Column 3: no rule, with 5× greater misclassification revealed upon longitudinal follow up Odds ratio (95% CI)	Column 4: 3-year rule Odds ratio (95% CI)	Column 5: sliding 5-year rule Odds ratio (95% CI)
50	33	3.17 (1.26, 7.93)	2.25 (0.98, 5.17)	1.80 (0.83, 3.90)	1.45 (0.68, 3.13)	2.00 (0.94, 4.27)
50	25	4.40 (1.67, 11.62)	2.71 (1.14, 6.46)	2.11 (0.96, 4.67)	1.70 (0.78, 3.71)	2.44 (1.13, 5.31)
50	20	12.00 (2.84, 50.77)	5.25 (1.80, 15.29)	3.50 (1.41, 8.67)	2.57 (1.07, 6.16)	3.83 (1.56, 9.41)
50 (with gradient of exposure for partner according to time to onset)	10	7.67 (2.30, 25.53)	3.17 (1.26, 7.93)	2.25 (0.98, 5.17)	2.83 (1.12, 7.19)	3.67 (1.49, 9.04)

column (column 2), a longer follow up was assumed, such that three times as many of the co-twins in initially discordant pairs became demented longitudinally (n = 15 pairs selected at random from the discordant pairs in the 'no rule' group). In the second additional column (column 3), even greater longitudinal change in concordance was assumed, with co-twins in 25 initially discordant pairs assumed to have become demented longitudinally. Columns 4 and 5 show results under the 3-year rule and sliding 5-year rule.

For purposes of modeling the exposure, first, 50% of all individuals eventually diagnosed with dementia were randomly designated as exposed, whilst 33% of those individuals without dementia were randomly designated as exposed. For each discordancy rule, odds ratio estimates of relative risk for matched pairs were calculated, based on pairs discordant for both dementia and exposure. The analysis was repeated designating 50% of dementia cases as exposed and 25% of individuals without dementia, then designating 50% of dementia cases as exposed and 20% of individuals without dementia. Employing no rule resulted in higher odds ratios in each of the scenarios than either of the rule conditions. Only under the last scenario did the 3-year rule indicate a significant risk attached to the exposure. The sliding 5-year rule was intermediate in sensitivity, indicating a significant odds ratio under both the 50–25% and the 50–20% exposure scenarios. The same pattern was found with a new randomization, and if exposures were set lower for both dementia cases and cognitively intact individuals. Importantly, considering the columns in which more pairs from the 'no rule' group are assumed to become concordant over time, the difference between no rule and the constrained rules decreases.

Finally, we modeled an alternative scenario, where it was assumed that exposure to the risk factor did not act simply on occurrence versus non-occurrence of disease, but rather on age of onset, such that discordancy for exposure would decrease twin similarity for age of onset. Individuals with dementia were randomly assigned to a level of exposure based on intrapair similarity for age of onset. A 50% exposure was assigned to the first member of each pair to become demented (or to both twins if age of onset was the same). Among co-twins who remained cognitively intact, 10% were designated as exposed. Co-twins who became demented greater than 7 years after the proband's onset were given a 20% rate of exposure; co-twins who became demented 4 to 7 years later were given a 30% rate of exposure; with an interval of 3.5 years or less, co-twins were given a 40% rate of exposure. Under this model, the rules behaved more similarly. In short, comparing different rules depends in part on the mechanisms entailed in how exposures affect disease onset.

Discussion

Researchers using a matched pair design have typically failed to describe their criteria for establishing that the pairs are discordant for the disorder being studied. Late-onset disorders present particular challenges to defining discordancy. We have proposed an alternative approach that might be applied in such studies.

With late-life disorders, all studies of discordant pairs implicitly include pairs that may eventually become concordant. Having analyses based on controls who eventually become affected is equivalent to the issue of misclassification in classical epidemiology. Normally, one would expect misclassification to result in less ability to find a significant effect. Indeed, our simulation demonstrated that greater

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misclassification would result in a nearly two-fold decrease in the odds ratio. The 'no rule' method, when based on our relatively small sample, results in greater risk estimates than any other method, suggesting that if there is little misclassification (ie little likelihood that intact co-twins in initially discordant pairs will become affected), then the implicit rule is acceptable. This assumption, however, may not be tenable in studies of dementia.[16]

In studies of late life disorders, matched pairs studies may more correctly be construed as searching for environmental exposures that affect age of onset within pairs. However, only one systematic approach to this problem has previously been proposed.[17] We offer criteria that both (a) count pairs who eventually become concordant among the discordant pairs, if they have remained discordant sufficiently long, and (b) allow for death as an alternative outcome. Indeed, the simulation indicates that the sliding 5-year rule provides acceptable results, and potentially allows more pairs to be considered for analysis. It should be noted that the sliding 5-year rule described here is designed for a matched pair design and would not necessarily be recommended for purposes of analyses of heritability. Lastly, different rules might be developed for other disorders, for example, where onset is more abrupt, as would be evidenced by clinical evidence and life-table analysis.

Acknowledgements

This work is supported by National Institutes of Health Grants No. R01-AG08724 and AG10175 and the Swedish Council for the Planning and Coordination of Research.

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