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Changes in the DZ Unlike/Like Sex Ratio in The Netherlands

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Abstract. Based on Dutch twin incidence figures since the beginning of the current century, evidence is provided in support of the idea that the DZ unlike/like sexed ratio has gradually shifted (since 1900) from unity to less than unity. Opposing conclusions with regard to the justification of the use of Weingberg's differential rule are very probably correct in themselves but could depend on country and period of birth of the twin sample used. Furthermore, the fast drop and subsequent rise in DZ twinning rate between about 1963 and 1990 can very likely for the greater part be ascribed to a parallel shift in maternal age.

Key words: Weinberg's rule, Twinning rate, Sex ratio

INTRODUCTION

The question with regard to the validity of Weinberg's differential rule for epidemiological use in monozygotic (MZ) and dizygotic (DZ) twinning rates [10,11] is a recurring issue in twin research. This has to do with the doubt about one of the basic assumptions underlying the rule, viz, that the number of like-sex DZ twin pairs equals that of unlike-sex pairs. If, for instance, the DZ like-sex frequency exceeds that of the DZ unlike-sex frequency, then the total DZ frequency is underestimated and the MZ frequency will be overestimated accordingly. Suspects that this could actually be the case have been expressed by Renkonen [8], Nylander and Corney [7] and James [5]. The latter author combined the results of four other studies, comprising a total of 972 twin pairs for which both sex and concordance/discordance of the same set of blood markers were known. Within the (critical) category of twin pairs that were discordant for blood typing, 453

pairs were like-sexed and 389 unlike-sexed. In other words, there appeared to be an excess of like-sexed pairs of DZ twins relative to the number of pairs of opposite sex.

Eight years later James [6] arrived at the same conclusion by counting the total number of like-and unlike-sex DZ twins in six different British and American studies (zygosity-typing based on autosomal markers alone): from a total of 1334 DZ twin pairs, 725 were of the same sex type and 609 of the opposite sex type. Expected values were 674 and 660, respectively. A significant deviation.

Other studies [3,9] strongly oppose James' conclusion. The study by Vlietinck et al [9] is in this respect a very powerful one, since it is based on more than 2500 twin pairs of known zygosity and placentation. These authors conclude that Weingberg's differential rule is all right and can be safely used.

One of the prerequisites that should hold if Weinberg's rule is correct, is that the time series of DZ and MZ frequencies are independent, ie, over the years the correlation between MZ and DZ rate should be zero, since the underlying mechanisms of DZ and MZ genesis are unrelated. Only if some common external factor would influence both frequencies or if the assumption about equality of DZ like-sex and unlike-sex frequencies is incorrect, a correlation between the two time series can be expected Dutch twin figures were considered for the presence of relatedness of DZ and MZ incidence.

RESULTS AND DISCUSSION

DZ and MZ twin frequencies for the Netherlands are available since 1904. These frequencies are calculated with Weinberg's rule, based on the opposite-sex twin frequency. The MZ and DZ time series (N = 87) appeared to be significantly correlated: r(Pearson) = − 0.69. For Denmark, Sweden and Norway these correlations were calculated over shorter periods (not all figures for the same period as in the Netherlands were available). These correlations were $r = -0.42$ (1910-1985); $r = -0.56$ (1961-1985) and $r = -0.12$ (1931-1985), respectively.

Smoothed MZ and DZ time series are presented in Fig. 1. DZ frequency can be read on the left y-axis and MZ frequency on the right one. The MZ axis has been amplified relative to the left DZ axis, so that maximum and minimum of both time series occupy the same distance on either axes. The years 1904-1906 have been left away after smoothing, because these frequencies in the beginning of a time series are disproportionally represented in the smoothing result.

Fig. 1 shows a very slow, global increase of MZ frequency from the beginning of the century till now and a comparable decrease over the same period of DZ frequency (apart from the large dip during the 1960s and 1970s, seen in all industrialized countries, which is in our opinion a separate phenomenon to be considered later on).

Roughly spoken, there is a *relative* superiority of DZ frequency over MZ frequency before (about) World War II, "normal" MZ and DZ rates between about 1945 and 1960, and a *relative* superiority of MZ frequency over DZ frequency after about 1960.

This *could* mean that — as far as the Netherlands are concerned — the presumed DZ like-sexed excess (leading to underestimation of total DZ twinning rate and overestimation of MZ twinning rate) is correct only for the post-1960 period. During the pre-1945 period the opposite (ie, excess of unlike-sexed DZ twinning rate) might have been

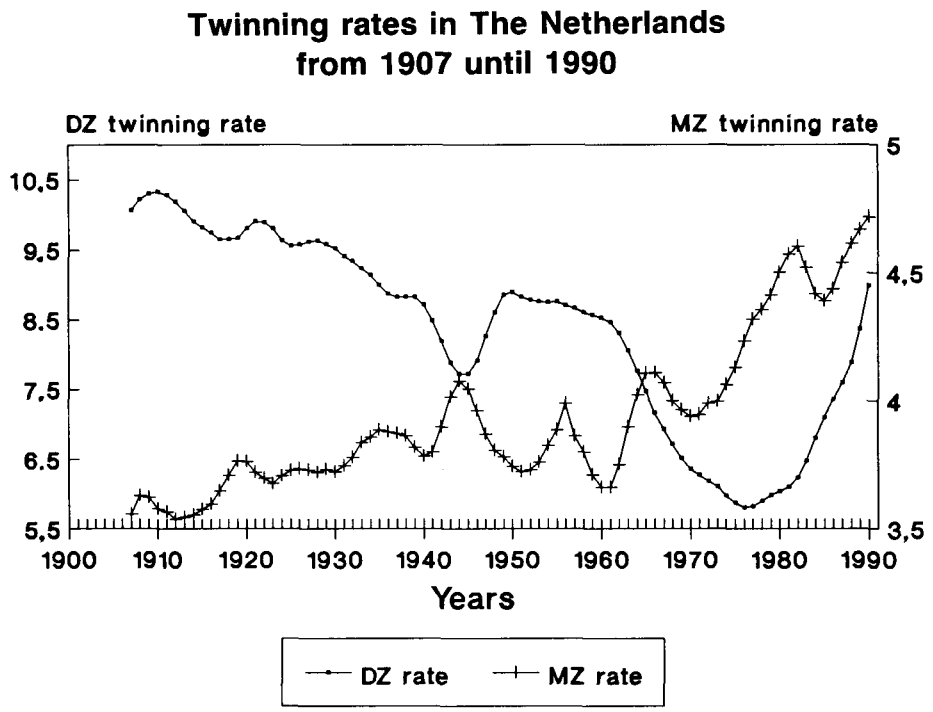

Fig. 1. Smoothed trends in DZ (left y-axis) and MZ (right y-axis) twinning rates from 1907 until 1990 in the Netherlands per 1000 maternities.

true. Or, in other words, the DZ-like/unlike-sexed ratio is not constant and varies from time to time and between populations. This latter feature has been demonstrated by Allen and Hrubec [1].

As said before, the striking fall in DZ rate during the 1960s and 1970s followed by a marked recovery during the last decade, is very likely a separate phenomenon, because it is much stronger and faster than the very slow trend since 1904 and not correlated with MZ rate during the same period. Very probably, this large DZ dip is caused by a parallel shift in average maternal age. Fig. 2 shows the DZ twinning rate from 1968 until 1990 (actually this is an enlargement of a part of Fig. 1) on the right y-axis and the proportion of children delivered by mothers of 30 years and older on the left y-axis. It is a known fact that, up to the maternal age of about 40 years, there is an increasing, nearly linear trend of DZ twinning rate; beyond that age there is a rather abrupt decline [1,2,4]. Therefore, the marked parallel between these two trends over the years strongly suggests that change in mean maternal age is the main cause of change in DZ rate during the last couple of decades.

In conclusion, we can say that the MZ twinning rate is slowly but consistently rising and the DZ twinning rate falling, a fast drop in DZ rate followed by a fast increase dur-

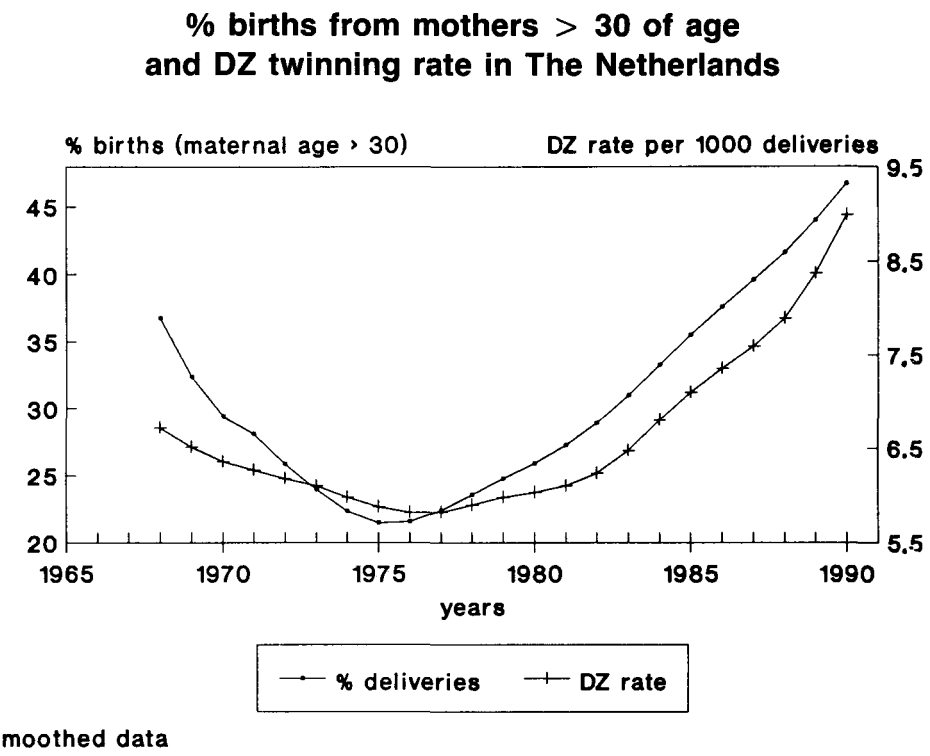

Fig. 2. Smoothed trends in percentage of deliveries by mothers of 30 years and older (left y-axis) and DZ twinning rate (per 1000 maternities; right y-axis) from 1968 until 1990.

ing the last decades being superimposed upon this slow decline. This latter fast change can very likely be ascribed to contigent changes in maternal age.

Confining ourselves to the slow changes in both MZ and DZ twinning rate, and combining this with the high correlations between these two biologically unrelated time series, the conclusion is warranted that since the beginning of the century the DZ unlike sexed/like sexed ratio has shifted from larger than unit to smaller than unity. If this is correct, then MZ rate was underestimated before about World War II and DZ rate was overestimated accordingly, whereas the opposite miscalculations were made during the last three decades or so, anyhow in the Netherlands. The peculiarities of twin epidemiology in a certain country will determine the nature of the twin samples drawn from it and so the conclusion with regard to the justification of the use of Weinberg's rule. If this line of reasoning is correct, the problem remains why the DZ-like sex/unlike sex ratio is not constant and which conditions influence changes in this ratio. Whatever the answer may be, caution with regard to the use of Weinberg's differential rule is necessary.

Finally, we think that the strong rise in maternal age accounts for the greatest part of the increase in total twinning rate, ovulation induction and in vitro fertilization being only secondary causes. The latter factors seem however to be very important in their

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contribution to the sharp increases in triplet and quadruplet birth rates: in the Netherlands, these types of multiples have increased by about 400%, over the last 15 years, whereas the total twinning rate increased by no more than about 25 to 30% over the same period. As said, this growth is very likely for the greater part ascribable to the increase in maternal age.

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