

## A note on Fisher's 'average effect' and 'average excess'

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*(Received 16 May 1985)*

The average effect and average excess of a gene substitution are formulated in terms of gene frequencies and inbreeding coefficient. This clarifies their meanings and shows how each is affected by non-random mating. The meanings of various definitions are examined, and one commonly used definition of average effect is found to be invalid with non-random mating. The concept of breeding value is shown to have no useful meaning when mating is not random.

The 'average effect' of a gene substitution is fundamental to quantitative genetics and its meaning in a random mating population is well understood. Fisher's parallel idea of the 'average excess' is, however, less well understood. Fisher (1930) introduced the two concepts for developing his 'Fundamental Theorem' (see Price, 1972), which deals with the change of mean fitness resulting from natural selection. The consequence of selection can be thought of in two stages. Selection, due to differences of fitness between the genotypes, causes a difference of gene frequency between the selected parents and the population to which they belong. This difference of gene frequency is proportional to the average excess. The gene frequency in the offspring is the same as that of the parents, and the change of gene frequency from one generation to the next causes a change of mean. The change of mean of any quantitative character consequent on the change of gene frequency is proportional to the average effect. (These changes due to selection will be stated more fully later.) The average effect and average excess are equal to each other under random mating, so the distinction between them does not often matter in practice. With non-random mating they differ, but it is not easy to discover from Fisher's writings, or from current text books, how they differ and how they are affected by departures from Hardy–Weinberg genotype frequencies.

The average effect and average excess can each be defined or described in two ways. Under random mating, when the average effect and average excess are equal, they are all valid definitions of either quantity. With non-random mating, however, one of the definitions is no longer valid for either the average effect or the average excess, a point that does not seem to be generally known. The purpose of this note is to demonstrate the meanings of the different definitions and to show in a simple manner how non-random mating affects the two quantities. Those who already understand average effect and average excess will find nothing new here;

all that is done is to bring together and simplify algebraic relationships that can be found in texts such as Kempthorne (1957), Crow & Kimura (1970), Edwards (1977) or Ewens (1979).

The symbols to be used here for gene frequencies, genotypic values of any quantitative character, and genotype frequencies are shown in Table 1. The average effect will be denoted by  $\alpha$  and the average excess by  $e$  (in place of Fisher's  $a$ , which is used here for genotypic values). The simplification comes from considering a population in which departures from Hardy-Weinberg genotype frequencies can be expressed in terms of an inbreeding coefficient,  $F$ . The average effect and average excess were expressed in this way by Kempthorne (1957). The gene frequencies,  $p$  and  $q$ , refer to the population as a whole, and the genotype frequencies in the whole population are expressible in terms of  $p$ ,  $q$  and  $F$  as in Table 1 (see Falconer, 1981, p. 61). The average effect and average excess refer also to the population as a whole, with the particular breeding structure described by its value of  $F$ .

An average effect can be assigned to each allele of a multiallelic locus; each is a difference from the population mean. When there are only two alleles the difference between their average effects is called the average effect of the gene substitution. If  $\alpha_1$  and  $\alpha_2$  are the average effects of the alleles  $A_1$  and  $A_2$  respectively, then the average effect of the gene substitution,  $\alpha$ , is

$$\alpha = \alpha_1 - \alpha_2. \quad (1)$$

In the same way an average excess can be assigned to each allele or to the gene substitution. For simplicity only a two-allele locus will be explicitly considered in what follows, and the average effect or average excess will be expressed as that of the gene substitution. We may, however, note the following relationships, which will be used in a later section. Since each allelic effect is a deviation from the mean, the mean of the allelic effects must be zero, i.e.

$$p\alpha_1 + q\alpha_2 = 0.$$

From this and (1) above it follows that

$$\left. \begin{aligned} \alpha_1 &= q\alpha \\ \alpha_2 &= -p\alpha \end{aligned} \right\}. \quad (2)$$

The same relationships hold for average excesses.

When mating is random and the genotypes are in Hardy-Weinberg proportions the average effect and the average excess of a gene substitution are, in the notation of Table 1,

$$\alpha = e = a + d(q - p). \quad (3)$$

(See Falconer, 1981, p. 106.) We can now consider how this expression is modified when mating is non-random.

For considering the meanings of the two quantities it will be more convenient to start with the average excess. The nature of the four definitions referred to earlier can be briefly stated thus: (A) weighted mean of genotypic values; (B) values transmitted in gametes; (C) regression of value on gene-dosage; (D) effect of allele

replacement. When mating is random all four definitions are equivalent, and define equally the average excess and the average effect. When mating is non-random, (A) and (B) define the average excess, (C) defines the average effect, but (D), as we shall see, defines neither.

Table 1

Genotype	Value	Frequency
$A_1A_1$	$a$	$P = p^2(1-F) + pF$
$A_1A_2$	$d$	$H = 2pq(1-F)$
$A_2A_2$	$-a$	$Q = q^2(1-F) + qF$
Population mean: $M = a(P-Q) + Hd$ $= a(p-q) + 2pqd(1-F)$		
Gene (allele)	$A_1$	$A_2$
Gene frequency	$p$	$q$

*Definition (A): Average excess*

The definition of average excess given by Fisher (1941) may be paraphrased as follows. Divide the population into two groups, one containing all  $A_1A_1$  homozygotes and half of the heterozygotes, the other containing all  $A_2A_2$  homozygotes and half the heterozygotes. Find the mean genotypic value of the individuals in each group. The difference between these means is the average excess of the gene substitution. This is equivalent to taking the difference between the weighted mean of individuals carrying  $A_1$  and the weighted mean of individuals carrying  $A_2$ , the weighting being by the frequency of the allele in the genotype, i.e. 1 or  $\frac{1}{2}$ . Symbolically,

$$e = \frac{Pa + \frac{1}{2}Hd}{P + \frac{1}{2}H} - \frac{Q(-a) + \frac{1}{2}Hd}{Q + \frac{1}{2}H}. \quad (4)$$

To reduce this expression to a meaningful form, first substitute

$$\left. \begin{aligned} P + \frac{1}{2}H &= p \\ Q + \frac{1}{2}H &= q \end{aligned} \right\} \quad (5)$$

This, after some rearrangement, leads to

$$e = \frac{a(Pq + Qp) + \frac{1}{2}Hd(q-p)}{pq}.$$

Now replace  $P$ ,  $Q$  and  $H$  by their equivalents in terms of  $p$ ,  $q$  and  $F$  from Table 1. This yields the following equalities

$$\left. \begin{aligned} Pq + Qp &= pq(1+F) \\ \frac{1}{2}H &= pq(1-F) \end{aligned} \right\} \quad (6)$$

and when these are substituted the average excess of the gene substitution becomes

$$e = a(1+F) + d(q-p)(1-F). \quad (7)$$

This reduces to expression (3) when mating is random ( $F = 0$ ).

The average excess of each allele separately is the deviation of each group from the population mean: the average excess of  $A_1$  is the weighted mean of individuals carrying  $A_1$  as a deviation from the population mean.

*Definition (B): Average excess*

Fisher (1941) further explains the meaning of average excess as follows (my symbols): 'Thus, if gametes bearing  $A_1$  or  $A_2$  are chosen at random, and the zygotes to which they ultimately give rise are measured, the average for those bearing  $A_1$  will exceed the average for those bearing  $A_2$  by the difference  $e$ .' This definition applied to a random mating population is commonly used to explain the idea of average effect, because it seems the easiest way to grasp the meaning of breeding value, as the value transmitted in the gametes. Edwards (1982), however, referring to my use of it (Falconer, 1981, p. 104), pointed out that it is strictly speaking a definition of average excess, not average effect, though the distinction is irrelevant in a random mating population. Let us verify the meaning. Uniting with other gametes according to the mating system of the population,  $A_1$  gametes must unite with another  $A_1$  gamete so as to produce all the  $A_1A_1$  zygotes, whose frequency is  $P$  in the whole population. The chosen  $A_1$  gametes will unite with  $A_2$  gametes so as to produce half of the  $A_1A_2$  zygotes. The total frequency of  $A_1$  gametes is  $p$ . Therefore the mean of the progeny produced by gametes carrying  $A_1$  is

$$\frac{Pa + \frac{1}{2}Hd}{p}$$

Similarly the mean of the progeny produced by gametes carrying  $A_2$  is

$$\frac{Q(-a) + \frac{1}{2}Hd}{q}$$

and the difference is the average excess of the gene substitution,  $e$ , as in expression (4) derived from definition (A).

This definition (B) may seem to suggest that breeding values will be expressed in terms of the average excess when mating is non-random. This, however, is not the case, for reasons that will be given later.

*Definition (C): Average effect*

The average effect of a gene substitution is defined by Fisher (1941) as the linear regression coefficient of genotypic value on the number of  $A_1$  alleles in the genotype, i.e. 2, 1 or 0, which may be called the gene dosage. The calculation of the regression in terms of the quantities in Table 1 may be outlined as follows. Let  $y$  be the genotypic value and  $x$  the gene dosage, as in Table 2. Then

$$\text{cov}_{yx} = 2aP + dH - 2p[a(P - Q) + dH].$$

Rearrangement leads to

$$\text{cov}_{yx} = 2a(Pq + Qp) + dH(q - p)$$

and writing  $P$ ,  $Q$  and  $H$  in terms of  $p$ ,  $q$  and  $F$  from Table 1, with the help of (6), gives

$$\text{cov}_{yx} = 2pq[a(1+F) + d(q-p)(1-F)],$$

which by (7) is

$$\text{cov}_{yx} = 2pqe. \quad (8)$$

The variance of  $x$  is

$$\sigma_x^2 = 4P + H - 4p^2,$$

which reduces eventually to

$$\sigma_x^2 = 2pq(1+F) \quad (9)$$

Table 2

	Frequency	$y$	$x$
$A_1A_1$	$P$	$a$	2
$A_1A_2$	$H$	$d$	1
$A_2A_2$	$Q$	$-a$	0
Means		$a(P-Q) + dH$	$2p$

Dividing (8) by (9) gives the regression of  $y$  on  $x$ ,  $b_{yx}$ . This, by the definition, is the average effect, so

$$\alpha = b_{yx} = \frac{e}{1+F}. \quad (10)$$

Substituting for  $e$  from (7) gives the average effect of a gene substitution as

$$\alpha = a + d(q-p) \left[ \frac{1-F}{1+F} \right]. \quad (11)$$

This reduces to expression (3) when mating is random ( $F = 0$ ). We may note that if the regression is calculated on the gene dosage of  $A_2$  rather than of  $A_1$  the result is the same but of opposite sign.

The value of a genotype predicted from the linear regression is called its additive (or genic) value. Thus the average effect of the gene substitution is the difference of additive value between the genotypes  $A_2A_2$  and  $A_1A_1$ , or between  $A_1A_2$  and  $A_1A_1$ . The additive value of a genotype as a deviation from the population mean is the sum of the average effects of the alleles in the genotype. For a clear graphical explanation of the regression definition, see Edwards (1977, p. 14).

#### *Summary of relationship between $e$ and $\alpha$*

Before proceeding to the last definition it may be useful to recapitulate the formulae showing the relationship between average excess and average effect, and how each is affected by non-random mating.

When mating is random the average excess and average effect of a gene substitution are equal and are given by

$$e = \alpha = a + d(q-p). \quad (3bis)$$

When mating is non-random the average excess is

$$e = a(1 + F) + d(q - p)(1 - F) \tag{7 bis}$$

and the average effect is

$$\alpha = a + d(q - p) \left[ \frac{1 - F}{1 + F} \right]. \tag{11 bis}$$

Thus there is a very simple relationship between the two quantities, which is

$$e = \alpha(1 + F), \tag{12}$$

as shown by Kempthorne (1957, p. 347), and already seen in (10) above.

The following further points may be noted. When the population is completely inbred ( $F = 1$ ),  $e = 2a$ , which is the homozygote difference in value; and  $\alpha = a$ , which is half the homozygote difference. When there is no dominance ( $d = 0$ ) the average effect is unaffected by non-random mating and  $\alpha = a$ . The average excess, however, is affected by non-random mating even when there is no dominance.

*Definition (D)*

Fisher (1941; 1958, pp. 31 and 35) explains the meaning of the average effect of a gene substitution as the change of mean value that would result from changing one allele into the other, as if by mutation, the gene to be changed being chosen at random in the existing genotypes. Applied to a random mating population, this is a valid definition of average effect (or equally of average excess), and is used by Kempthorne (1957, p. 310), Crow & Kimura (1970, p. 117), and Falconer (1981, p. 104). Fisher gives it as an explanation of average effect without restriction to random mating, but he does not use it to formulate the average effect in terms of genotype frequencies. When mating is non-random, however, it is not equivalent to definition (C) above, as we shall now see.

There are two procedures for carrying out the imaginary replacement of one allele by another. One gives the 'effect' of the gene substitution, and the other gives the 'effect' of each allele separately. Neither gives the average effect defined by (C), except under random mating or if there is no dominance.

The first procedure, which seems to be what Fisher intended, though he does not describe the procedure precisely, is as follows.  $A_2$  alleles in the existing genotypes are chosen at random and replaced by  $A_1$  alleles. The mean change of value consequent on the gene replacement is the 'effect' of the gene substitution. The meaning of the 'effect' can be worked out as follows. Table 3 sets out the

Table 3

Genotype	Frequency	Value	Replacement by $A_1$		Replacement by $A_2$	
			New value	Change	New value	Change
$A_1A_1$	$P$	$a$	$a$	0	$d$	$-(a - d)$
$A_1A_2$	$H$	$d$	$a$	$a - d$	$-a$	$-(a + d)$
$A_2A_2$	$Q$	$-a$	$d$	$a + d$	$-a$	0

genotype frequencies and values, and the change of value when one allele is replaced by the other. When  $A_2$  is replaced by  $A_1$  the total frequency of such replacements is  $q$ , the frequency of  $A_2$ . The mean change of value which we shall call  $D_1$ , is

$$\begin{aligned} D_1 &= \frac{Q(a+d) + \frac{1}{2}H(a-d)}{q} \\ &= \frac{a(Q + \frac{1}{2}H) + d(Q - \frac{1}{2}H)}{q} \\ &= \frac{aq + d[(q^2 - pq)(1-F) + qF]}{q} \\ &= a + d[(q-p)(1-F) + F]. \end{aligned}$$

This is not the average effect except when  $F = 0$  or in the absence of dominance ( $d = 0$ ).

Now consider the reverse change, replacing  $A_1$  alleles by  $A_2$ . The consequent mean change of value,  $D_2$ , is

$$D_2 = \frac{-P(a-d) - \frac{1}{2}H(a+d)}{p},$$

which reduces to

$$D_2 = -\{a + d[(q-p)(1-F) - F]\}.$$

Note that  $D_2$  is not equal to  $-D_1$ , i.e. changing  $A_1$  into  $A_2$  gives a reduction of mean value that is not the same as the increase resulting from changing  $A_2$  into  $A_1$ . That this must be so can be seen by considering a completely inbred population, when all changes are from one or other homozygote to heterozygote. If, however, we take the weighted difference, weighting by the frequency of the allele to be replaced, we get

$$qD_1 - pD_2 = a + d(q-p),$$

which is the average effect of the gene substitution under random mating, irrespective of the actual mating system.

The second procedure for gene replacement is as follows. Any gene is chosen at random from the genotypes in the population, and is replaced by  $A_1$ . If the gene chosen for replacement is already  $A_1$  there is no consequent change of value, but this is to be counted in the mean of all replacements. The mean change of value is the 'effect' of the  $A_1$  allele. If the genotypes are in Hardy-Weinberg proportions this is the average effect,  $\alpha_1$ , of the  $A_1$  allele (Crow & Kimura, 1970, p. 117). This procedure differs from the first only in that the total frequency of replacements is now 1 instead of  $q$ . Therefore the mean change consequent on replacing any gene by  $A_1$  is

$$D'_1 = Q(a+d) + \frac{1}{2}H(a-d),$$

which reduces to

$$D'_1 = q\{a + d[(q-p)(1-F) + F]\}.$$

The reverse change, resulting from replacing any gene by  $A_2$ , is

$$D'_2 = -p\{a + d[(q-p)(1-F) - F]\}.$$

Neither of these changes is the average effect of the allele. Note that  $D'_1 = qD_1$  and  $D'_2 = pD_2$ . Thus the simple difference between the two changes by the second procedure is the same as the weighted difference by the first procedure, and gives the average effect of the gene substitution under random mating, irrespective of the actual mating system.

Fisher uses the imaginary replacement of one allele by another as a verbal description to introduce the idea of average effect, and it seems to have been seen by him as the basis for the concept. It is therefore surprising to find that it is valid only under random mating or in the absence of dominance.

### *Variance*

The idea of additive genetic variance is based on average effects as defined by (C) above, and is the variance of additive values. For a locus with two alleles the additive values of the three genotypes, as deviations from the population mean, are

$$A_1A_1: 2\alpha_1 = 2q\alpha$$

$$A_1A_2: \alpha_1 + \alpha_2 = (q-p)\alpha$$

$$A_2A_2: 2\alpha_2 = -2p\alpha.$$

With the genotype frequencies in Table 1, the additive variance arising from this locus works out to be

$$V_A = 2pq\alpha^2(1+F). \quad (13)$$

Alternatively, the additive variance due to a locus with two alleles may be defined as the variance removed by regression of genotypic value on gene dosage (Kempthorne, 1957, p. 311). The variance removed can be calculated as  $b_{yx} \text{cov}_{yx}$ . So, from (10) and (8), the additive variance is

$$V_A = 2pqe\alpha. \quad (14)$$

This is the form in which Fisher (1941, 1958) writes the additive variance (which he calls the genetic variance). Substituting for  $e$  from (9) gives

$$V_A = 2pq\alpha^2(1+F)$$

as in (13) above. The  $\alpha$  here is, of course, the  $\alpha$  appropriate to the value of  $F$  as given by (11), and not the random mating value. In the absence of dominance, however,  $\alpha = a$  and is unaffected by  $F$ . The variance arising from an additive locus is therefore

$$V_A = 2pq\alpha^2(1+F).$$

This is the familiar expression saying that the variance due to additive genes is  $(1+F)$  times the variance due to those genes in a random mating population (see Kempthorne, 1957, p. 367).

### *Response to selection*

It was said at the beginning that the response to selection can be divided into two stages, the change of gene frequency which is proportional to the average excess, and the consequent change of mean value which is proportional to the average effect. The response in these two stages can be deduced as follows.



The change of gene frequency,  $\Delta p$ , can be predicted from the regression of gene frequency on value. Let  $S$  be the selection differential, i.e. the difference of mean value between the selected parents and the population to which they belong. Then

$$\Delta p = b_{py} S,$$

where  $b_{py}$  is the regression of gene frequency on value. (The subscript  $y$ , used under definition (C) above, is retained here to mean any quantitative character.) The covariance of value with gene dosage was found in equation (8) to be  $\text{cov}_{yx} = 2pqe$ . The covariance with gene frequency, i.e.  $1, \frac{1}{2}$  or  $0$ , is therefore

$$\text{cov}_{py} = pqe \quad (15)$$

as shown by Price (1972, equation 5.2). Therefore

$$\Delta p = \frac{pqe}{\sigma_y^2} S, \quad (16)$$

where  $e$  is the average excess of the gene substitution in respect of the character selected.

Similarly, the change of mean value,  $\Delta y$ , consequent on the change of gene frequency can be predicted from the regression of value on gene frequency. The regression of value on gene dosage is the average effect, by definition. The regression on gene frequency is therefore

$$b_{yp} = 2\alpha.$$

Therefore

$$\Delta y = 2\alpha\Delta p. \quad (17)$$

Putting together (17) and (16) gives the predicted response to selection as

$$R = \Delta y = \frac{2pqe\alpha}{\sigma_y^2} S. \quad (18)$$

Now  $2pqe\alpha$  is the additive variance, and  $\sigma_y^2$  is the phenotypic variance. So we have

$$R = h^2 S,$$

as shown by Kimura (1958), where  $h^2$  is the ratio of additive genetic to phenotypic variance under the specified breeding system.

When the character,  $y$ , is fitness expressed as relative fitness,  $w$ , the selection differential is equal to the phenotypic variance (see Falconer, 1981, p. 311).\* From (18) therefore, the response of relative fitness to natural selection becomes equal to the additive variance, as required by Fisher's fundamental theorem. When applied to natural selection the average excess,  $e$ , in equations (15) and (16) is the average excess of relative fitness. If we write  $k$  for absolute fitness and  $w$  for relative fitness, so that  $w = k/\bar{k}$  and  $e_w = e_k/\bar{k}$ , then in terms of absolute fitness

$$\Delta p = pqe_k/\bar{k}$$

\* Equation (20.1) of Falconer (1981) is true only of relative fitness, not of absolute fitness as stated. It is easily seen that the derivation is wrong unless the total number of offspring ( $N$ ) is equal to the number of parents, so that the mean number of offspring per parent is one.

(see Crow & Kimura, 1970, pp. 179–180), and in terms of relative fitness

$$\Delta p = pqe_w.$$

### *Breeding values*

When mating is random the breeding value of a genotype is defined as the sum of the average effects of the two alleles in the genotype, which is the additive value as noted above. The usefulness of the concept is that the expected phenotypic value of the progeny is the mean of the breeding values of the two parents. This leads to the practical definition, which allows the breeding value of an individual to be measured: the breeding value of an individual is twice the deviation of its progeny from the population mean when the individual's mates are chosen at random, the mates then having an expected breeding value of zero. When mating is non-random it is tempting to think that the definition should say that the mates are to be chosen according to the breeding structure of the population. This, however, is not a useful definition for the following reason. Because of the correlation in respect of gene dosage between the individual and its mates, the expected breeding value of the mates is now not zero. In consequence, part of the deviation of the progeny is attributable to the mates and not to the individual whose breeding value is to be defined. From this it follows that if the breeding values of two mated individuals were defined in this way, the expected value of their progeny would not be the mean of their breeding values. The concept of breeding value therefore does not have any useful meaning when mating is non-random.

Furthermore, if we did want to calculate the expected value of the progeny, which would be needed for deducing the covariance of offspring with parents, we could not do so from a knowledge of  $F$  alone. To do so we would need to know the frequencies of the different mating types, and this needs more information about the breeding structure than is contained in the inbreeding coefficient. As an example we may consider a breeding structure in which a proportion of individuals inbreed, e.g. by selfing or sib-mating, while the remainder mate at random. Li (1976, p. 243) gives the mating-type frequencies in such a population when it is in equilibrium, with constant genotype frequencies. The expected values of the progenies of the three genotypes then work out to be as follows. In these expressions  $m$  is the correlation between mates in respect of gene dosage and is equal to  $2F/(1+F)$ .

$$\begin{array}{lll} A_1A_1: & qa(1+m) & + d[q(1-m) - 2pq(1-F)] = q[\alpha + m\{a - dp(1-F)\}] \\ A_1A_2: & \frac{1}{2}a(q-p)(1+m) & + \frac{1}{2}d[1 - 4pq(1-F)] \\ A_2A_2: & -pa(1+m) & + d[p(1-m) - 2pq(1-F)] = -p[\alpha + m\{a + dq(1-F)\}]. \end{array}$$

The progeny of the two homozygotes can be expressed somewhat more concisely, as shown on the right. It is clear that these cumbersome expressions are not simple functions of either the average effect or the average excess.

### *Uses of average excess*

In conclusion we may ask: how useful is the concept of average excess? We have seen its use in deriving the change of gene frequency resulting from selection (15)

from the covariance of value with gene frequency or gene dosage (8). And it provides a concise way of expressing the additive genetic variance when mating is non-random (14). When mating is random the distinction between average excess and average effect is not needed because the two have the same value, which is customarily referred to as the average effect. Fisher, as noted at the beginning, used the two quantities to derive his Fundamental Theorem. However, Price (1972, p. 138) says of the Fundamental Theorem that 'the derivation can be accomplished far more simply if we work entirely with regression coefficients and covariances without using Fisher's special "average excess" and "average effect" variables'.

I am indebted to Professors J. W. James, M. J. Wade and A. Robertson for much helpful advice.

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