Understanding the Regulation of Milk Fat Synthesis and Its Potential Application in Herd Management

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Introduction

There is growing interest in nutrition strategies focused on increasing the yield of milk components. The yields of milk fat and protein are the major contributors to the price that producers receive for milk. In an economic analysis assessing the value of milk components, a 5% increase in fat yield, protein yield, and milk yield increased net farm income by 13%, 15%, and 2%, respectively (St-Pierre, 2017). This reinforces the importance of focusing on increasing the yield of milk components and not milk yield per se to maximize milk price and income. Synthesis of milk fat in the mammary gland is a highly-coordinated process involving de novo synthesis of fatty acids (**FA**) and incorporation of preformed FA. Importantly, several factors can influence milk fat synthesis, including genetics (breed and selection), stage of lactation, parity, mastitis, dietary forage and grain levels, diet fermentability, dietary FA level and profile, and seasonal and regional effects. Furthermore, the potential utilization of milk FA as a management tool has recently received attention. We will briefly review the biological processes for milk fat synthesis, the interrelationship between different FA in the regulation of milk fat synthesis, and the potential for nutrition and management decisions based on milk FA analysis.

Milk Fat Synthesis

Milk FA originate from 1 sources: < 16 carbon FA are synthesized de novo in the mammary gland and > 16 carbon FA are extracted from plasma as preformed FA. Mixed FA (16-carbon FA) can be derived from either de novo or preformed sources. Acetate and β-hydroxybutyrate, formed by rumen fermentation of carbohydrates, represent the major carbon sources for FA synthesized de novo in the mammary gland (Bauman and Griinari, 2003). In plasma, FA absorbed from the intestine are transported in lipoproteins and FA mobilized from body tissues are transported as NEFA (Bauman and Griinari, 2003). Microbial synthesis of odd and branch chain FA in the rumen and absorption of biohydrogenation intermediates also contribute to the diversity of FA secreted in milk fat. A diagram representing the major metabolic pathways involved in milk fat synthesis is presented at Figure 1.

De novo FA synthesis: To produce milk FA from 4 to 16 carbons in length in the mammary gland, the main pathway involves acetate being converted to acetyl CoA by acetyl CoA synthetase. Next, acetyl-CoA carboxylase (**ACC**) converts acetyl-CoA to malonyl-CoA in an irreversible reaction (Bauman and Davis, 1974). The production of malonyl-CoA is considered the rate-limiting step for de novo synthesis of milk FA and the activity of ACC

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is considerably lower than the activity of other FA synthesis enzymes. β-hydroxybutyrate can also contribute carbons for initiating milk FA synthesis. In fact, Lin and Kumar (1972) indicated that the lactating mammary gland utilizes butyryl-CoA more efficiently than acetyl-CoA as a ''primer'' for FA synthesis. As shown by Palmquist et al. (1969), up to 50% of FA synthesized de novo by the lactating mammary gland utilizes β-hydroxybutyrate as the initial C4 methyl primer for FA synthesis. Propionate and branch chain volatile FA can be used as a primer for milk FA synthesis, leading to the synthesis of odd and branch FA (Palmquist, 2006). Acetate and β-hydroxybutyrate account for all carbons in C4:0-C12:0 milk FA, 75% of C14:0 and 50% of C16:0 (Smith et al., 1974). It is important to point out that although several precursors can initiate FA synthesis, acetyl-CoA is the principal building block that is used by the FA synthase (**FAS**) complex generating palmitate.

Besides a carbon source, FA synthesis requires NADPH. The activities of both citrate lyase and malic enzyme increase with high carbohydrate diets in non-ruminants. The activities of these latter enzymes are low in ruminants (Bauman et al., 1970), probably reflecting the greater availability of acetate as a lipogenic precursor in these species or the absence of the need to transport these units from the mitochondrion to the cytosol, or both. In ruminants, most of the glucose is derived from gluconeogenesis, while acetate, and other principal fuel molecules produced in the rumen provide the precursors for the initiation of lipogenesis in adipose tissue and the mammary gland.

Preformed FA: A second source of FA in the mammary gland is long chain FA from the diet and other tissues. The triglycerides (**TAG**) contained within chylomicrons and very low density lipoproteins (**VLDL**) in plasma are the primary source of milk FA >16 carbons in length taken up by the mammary gland (Palmquist, 2006) with NEFA also contributing FA to milk fat when concentrations of plasma NEFA are high, usually occurring during periods of negative energy balance in early lactation. Dietary FA, and FA formed during rumen biohydrogenation, are absorbed in the small intestine, esterified to glycerol forming relatively inert TAG and then packaged into TAG-rich lipoproteins that usually comprise chylomicrons or VLDL (Smith et al., 2006). Due to the large size of chylomicron and VLDL particles, they have little capacity to move across capillaries. Therefore, the movement of FA into the mammary gland depends on hydrolysis of the TAG within these particles, a process that is carried out by lipoprotein lipase (**LPL**) along the luminal surface of capillary endothelial cells (Smith et al., 2006). This process removes around 90% of the TAG from the particles, generating remnant lipoproteins that are largely taken up and removed by the liver (Drackley, 2000). Therefore, FA enter the cells either as FA released from the TAG-rich lipoproteins or FA within the albumin-FA pool. Free FA and diacylglycerol are taken up by mammary epithelial cells and used for TAG synthesis in the mammary gland.

Triglyceride synthesis: Milk fat is composed of 95 to 98% (**TAG**), 0.30 to 2.0% diacylglycerol, and small concentrations of phospholipids, cholesterol esters, and free FA (Jensen, 2002). The primary pathway used for synthesis of TAG in the mammary gland is the glycerol-3 phosphate pathway where both de novo and preformed FA are incorporated onto the glycerol-3 phosphate backbone. Glycerol phosphate acyl transferase (**GPAT**) is responsible for adding a fatty acyl-CoA to the sn-1 position of glycerol-3 phosphate and acyl glycerol phosphate acyl transferase (**AGPAT**)

adds the second fatty acyl-CoA to the sn-2 position. The final fatty acyl-CoA is added to the sn-3 position by diglyceride acyl transferase (**DGAT**) forming the TAG.

The location of FA along the glycerol backbone is not random with individual FA being preferentially located at different positions (Jensen, 2002). Interestingly, saturated FA are predominantly esterified at the sn-1 position and unsaturated FA at the sn-2 position (Jensen, 2002). Since C16:0 is the end product of de novo synthesis, it is potentially a key FA in this process. A higher preference (8- to 10-fold) was shown for C16:0 as a substrate for GPAT than C18:0 and *cis*-9 C18:1 in the mammary gland of dairy cows (Kinsella and Gross, 1973). Also, short- and medium-chain FA are preferentially esterified to the sn-3 position. Over 98% of C4:0 and 93% of C6:0 are esterified on the sn-3 position (Table 1; Jensen, 2002). The sn-2 position contains greater than 50% of all C10:0 to C14:0 milk FA. Distribution of C16:0 is uniform between the sn-1 and sn-2 position, while C18:0 is primarily esterified to sn-1 with a smaller proportion esterified to sn-3. *cis*-9 C18:1 is esterified to either the sn-1 or sn-3 position of TAG (Jensen, 2002).

Importantly, this control of FA placement within TAG provides the mammary gland with plasticity to secrete TAG into droplets that can be incorporated into milk and be fluid at body temperature (Dils, 1986; Jensen, 2002). Therefore, the control of melting point of milk fat is relatively constant even with large variations in the availability of FA with different melting points. The mechanisms by which the mammary gland controls the melting point of TAG include: increasing unsaturated FA by desaturation, the synthesis of short- chain FA, and preferentially positioning short-chain FA at the sn-3 position of the glycerol backbone.

Interdependence Between De Novo and Preformed FA During Milk Fat Synthesis

The concept of interdependence suggest that de novo synthesis may to a certain extent drive milk preformed FA yield, and vice versa, indicating a positive relationship between de novo and preformed milk FA. In a meta-analysis, Glasser et al. (2008) suggested that in low-fat diets, milk 18-carbon yield is probably limited by 18-carbon supply. Low 18-carbon availability may limit the incorporation of short- and medium-chain FA into milk TAG. The explanation for this likely lies at the mammary FA esterification steps, which involves both de novo synthesized FA and long-chain FA taken up from plasma. The production of diacylglycerols (mainly composed of long-chain FA), which are a substrate for DGAT, would remain low and would thus limit the incorporation of short- and medium-chain FA in milk TAG. In this context, increased dietary 18-carbon could act as primers for TAG synthesis and increase both de novo synthesis and 18-carbon incorporation into milk fat (Glasser et al., 2008).

We have recently investigated the relationship between the omasal flow of different FA and their effects on milk FA synthesis (de Souza et al., 2018a). Our analysis used individual observations (n=132) in lactating Nordic Red dairy cows from 9 Latin square or switch-back design studies. We observed a positive relationship between the omasal flow of C16:0 and total milk FA driven by an increase in the yield of de novo and mixed FA (Figure 2). Increasing C18:0 omasal flow did not affect the yield of de novo FA, but quadratically increased the yield of preformed and total FA in milk (Figure 3). For the flow of C18:0, maximum preformed and total FA yields were achieved when 18:0 flow was 1065 and 943 g/day respectively. Therefore, our results agree with the previous findings of Glasser et

al. (2008) demonstrating the interdependence between de novo synthesized FA and preformed FA and highlight that effects on de novo, mixed, and preformed milk FA is dependent upon the amount and profile of absorbed FA. Importantly, this interdependence between FA sources appears to mostly occur in dietary situations with low-risk for milk fat depression (**MFD**).

Substitution of Different Sources of Milk FA

In some instances, changes in milk fat yield to alterations in the supply of dietary FA may result in the substitution of different sources of milk FA, in which an increase in milk preformed FA yield coincides with a decrease in de novo FA yield. Grummer (1991) reported that an inverse relationship exists between the amount of fat supplemented in the diet and the concentration of de novo FA in milk fat. As more dietary fat is added, the proportion of de novo synthesized milk FA decreases, whereas the proportion of preformed milk FA increases. On a FA yield basis, the substitution effect of preformed de novo milk FA was recently reported by He and Armentano (2011) and He et al. (2012), who noted that the reduction in the yield of de novo milk FA was often compensated for by an increase in the yield of preformed milk FA when fat supplements were fed.

Similarly, Leonardi et al. (2005) indicated that increasing the fat content of distillers' grains with added solubles reduced de novo milk FA synthesis. However, the decreased yield of short-chain FA coincided with an increased yield of long-chain FA, resulting in no differences across treatments in total milk fat yield (Figure 4). Dorea and Armentano (2017) summarized the effects of five common dietary FA (C16:0, C18:0, *cis*-9 C18:1, *cis*-9, *cis*-12 C18:2, and *cis*-9, *cis*-12, *cis*-15 C18:3) on milk FA sources (de novo, mixed, and preformed). The results indicated that supplements rich in unsaturated FA decreased milk FA or caused substitution by inhibiting secretion of de novo milk FA with dietary *cis*-9, *cis*-12 C18:2 being the most inhibitory. Therefore, the substitution effect seems to occur when dietary interventions or management induce a 'mild MFD situation' and likely represents a lost opportunity since the substitution of different milk FA sources does not usually result in an increase in milk fat yield.

This is different to a 'classical' MFD situation which is characterized by a decrease in milk fat yield of up to 50%, with no change in milk yield or in the yield of other milk components (Bauman et al., 2011). During MFD, the profile of milk FA is markedly altered, and this is a characteristic of the biohydrogenation theory. We recently utilized a random regression model to analyze available individual cow data from 3 studies that induced MFD in dairy cows (unpublished results). We observed that as the degree of MFD increased, the concentration of de novo milk FA markedly decreased, while the concentration of preformed milk FA increased (Figure 4). However, on a yield basis, as the degree of MFD increased, the yield of de novo, mixed and preformed FA all decreased (Figure 5). Therefore, when evaluating the effects of nutrition and management strategies on milk FA profile, it is important to consider the unit that milk FA is reported in (concentration or yield basis), since this may impact the interpretation of results.

C16:0 Supplementation and Milk FA

We have recently carried out a series of studies examining the effect of individual saturated FA on production and metabolic responses of lactating cows. Most of our short-term studies involving C16:0 supplements (fed at 1.5 to 2.0% diet DM) have indicated increases in milk fat yield of ~100 g/day (Piantoni et

al., 2013; Lock et al., 2013; de Souza et al., 2018b). In long-term feeding, Mathews et al. (2016) observed that feeding a C16:0-enriched supplement (3.9% diet DM) over a 7-wk period also increased milk fat yield by ~200 g/day. Similarly, we recently observed that C16:0 supplementation consistently increased milk fat yield by 155 g/day compared with a non-fat control diet over a 10-wk supplementation period (de Souza and Lock, 2018). Although Rico et al. (2017) observed that maximum milk fat yield response occurred when C16:0 was fed at 1.5% of diet DM, the incorporation of C16:0 into milk fat increased linearly as C16:0 dose increased.

We recently utilized a random regression model to analyze available individual cow data from 13 studies that fed C16:0 supplements to dairy cows (unpublished results). We observed that C16:0 supplementation increased the concentration of mixed milk FA and reduced the concentration of de novo and preformed milk FA (Figure 6). On a yield basis, we observed that C16:0 supplementation increased the yield of mixed and total milk FA and did not change the yield of de novo and preformed milk FA (Figure 7). More importantly, we observed that C16:0 supplementation affected the yield of individual FA differently. The yield of milk C4:0 and C6:0 were positively associated with C16:0 supplementation while the yield of milk C12:0 and C14:0 were negatively associated with C16:0 supply. Dorea and Armentano (2017) summarized the effects of common dietary FA (C16:0, C18:0, *cis*-9 C18:1, *cis*-9, *cis*-12 C18:2, and *cis*-9, *cis*-12, *cis*-15 C18:3) on milk FA sources (de novo, mixed, and preformed). The results indicated that C16:0 supplementation increased total milk FA, mainly by increasing milk C16:0 yield, without affecting milk de novo and preformed yield. According to their regression of milk C16:0 yield on dietary FA, endogenous C16:0 contributes ~80% of total milk C16:0, but this proportion varies with the level and type of dietary FA fed.

Tzompa-Sosa et al. (2014) reported that the proportion of other FA at sn-2 was correlated with the total amount of C16:0 in the TAG. They suggested that an increase in availability of C16:0 for lipid synthesis in mammary epithelial cells will increase the activity of both isoforms of GPAT in the mammary gland. This increase in activity will then increase the proportion of C16:0 and other long-chain SFA acylated at sn-1 at the expense of sn-2. A decrease in the amount of long-chain saturated FA at sn-2 would be counterbalanced by other FA. Overall, this hypothesis could explain our finding that C16:0 increased the yield of mixed-source FA without reducing the yield of de novo and preformed FA, not only by increasing TAG synthesis but also by changing the FA interpositional distribution in the TAG.

Milk FA as a Herd Management Tool

Recently, the use of milk FA as a potential herd management tool has been proposed. In bulk tank milk samples from 430 commercial farms, Barbano et al. (2014) identified a positive correlation between de novo milk FA concentration and milk fat and true protein content. Similarly, Dorea and Armentano (2017) suggested that since milk mid-infrared analysis can be used to routinely measure the profile of milk FA, the concentration of different classes of milk FA may provide a good indication of inhibition of milk FA secretion.

Woolpert et al. (2016) investigated the relationship between de novo FA concentrations in bulk tank milk with management practices, dietary characteristics, milk composition, and lactation performance on commercial dairy farms. Farms were categorized as high (HDN; 26.18 ± 0.94 g/100 g of FA) or low de novo

(LDN; 24.19 ± 1.22 g/100 g of FA) FA in bulk tank milk. The authors reported that the yield of milk fat, true protein, and de novo FA per cow per day were higher for HDN versus LDN farms. The HDN farms had lower freestall stocking density (cows/stall) and higher feeding frequency than LDN farms. No differences between HDN and LDN farms were detected for dietary dry matter, crude protein, neutral detergent fiber, starch, or percentage of forage in the diet. However, dietary ether extract was lower for HDN than LDN farms.

In a subsequent study with a similar characterization of commercial dairy farms with HDN and LDN, Woolpert et al. (2017) detected no differences between HDN and LDN farms in the yield of milk fat or true protein. HDN farms tended to be more likely to deliver fresh feed twice versus once per day, have a freestall stocking density ≤110%, and provide ≥46 cm of feed bunk space per cow. There were no differences in forage quality or ration dry matter, crude protein, or starch content between HDN and LDN farms; however, ether extract was lower and physically effective fiber was higher for HDN farms.

Although the aforementioned results suggest that milk FA analysis may have potential as a management and nutritional tool, further research is needed to evaluate whether changes in management or nutritional strategies are related to milk FA and in which specific conditions. Importantly, it needs to be determined how well changes in milk FA on a concentration basis is related to changes in milk component yields.

Conclusions

The synthesis of milk fat in the mammary gland is a highly-coordinated process involving de novo synthesis of FA and incorporation of preformed FA. Importantly, milk FA interact by competitive and complementary mechanisms under different situations. We presented different scenarios in which changes in the supply of milk FA precursors can affect milk FA sources and the yield of milk fat. The interdependence between de novo synthesis and long-chain FA may to a certain extent drive milk preformed FA yield, indicating a positive relationship between de novo and preformed milk FA. The substitution effect seems to occur when dietary or management changes induce a 'mild MFD situation' and the substitution of different milk FA usually does not result in increases in milk fat yield. A 'classical' MFD situation when there is a decrease in milk fat yield is associated with a decrease in both de novo and preformed milk FA yields. Finally, when C16:0 supplements are fed, increased total milk FA yield is mainly driven by increasing milk C16:0 yield, without affecting the yields of de novo or preformed milk FA. Potentially, milk FA can be used to help monitor herd performance and farm decisions, but careful considerations should be given to other dietary factors, feed management, production level, and stage of lactation. Further research should be carried out to determine the utility of this analysis versus the use of more traditional dietary factors and milk component measures as important management benchmarks.

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Table 1. Positional distribution of different FA in milk TAG. Adapted from Jensen, (2002).

	sn-1	sn-2	sn-3
Milk FA mol/100 mol FA			
C4:0	1.6	0.30	98.1
C6:0	3.1	3.9	93.0
C8:0	10.3	55.2	34.5
C10:0	15.2	56.6	28.2
C12:0	23.7	62.9	13.4
C14:0	27.3	65.6	7.1
C16:0	44.1	45.2	10.5
C18:0	54.0	16.2	29.8
cis-9 C18:1	37.3	21.2	41.5

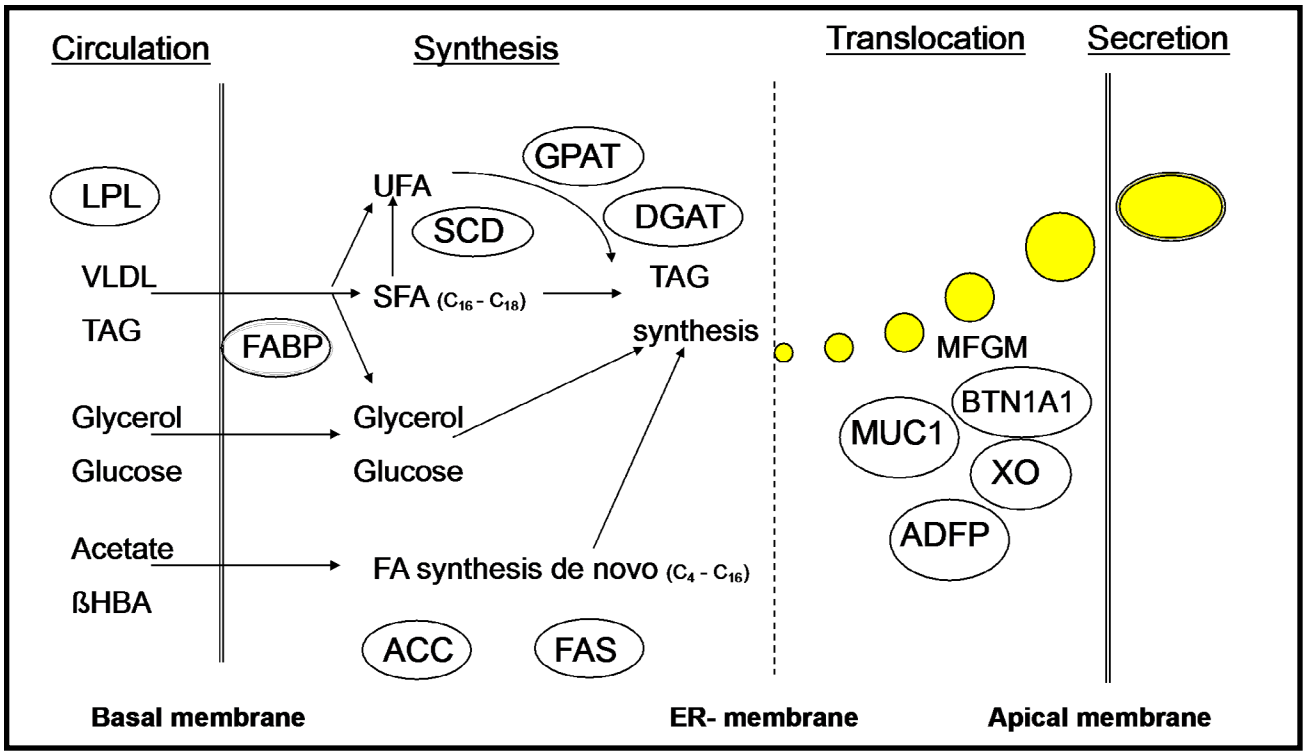

Figure 1. Diagram demonstrating the pathways involved in the synthesis and secretion of milk fat. Adapted from Bauman Lab (Cornell University). lipoprotein lipase (LPL); stearoyl-CoA desaturase (SCD); fatty acid transport proteins (FATP); glucose transporters (GLUT); glycerol phosphate acyltransferase (GPAT); diacylglycerol acyltransferase (DGAT); lipin (LPIN); fatty acid binding proteins (FABP); acetyl-CoA carboxylase (ACC); fatty acid synthase (FAS); mucin 1 (MUC1); butyrophilin (BTN1A1); xanthine oxidoreductase (XO) and adipophilin (ADPH).

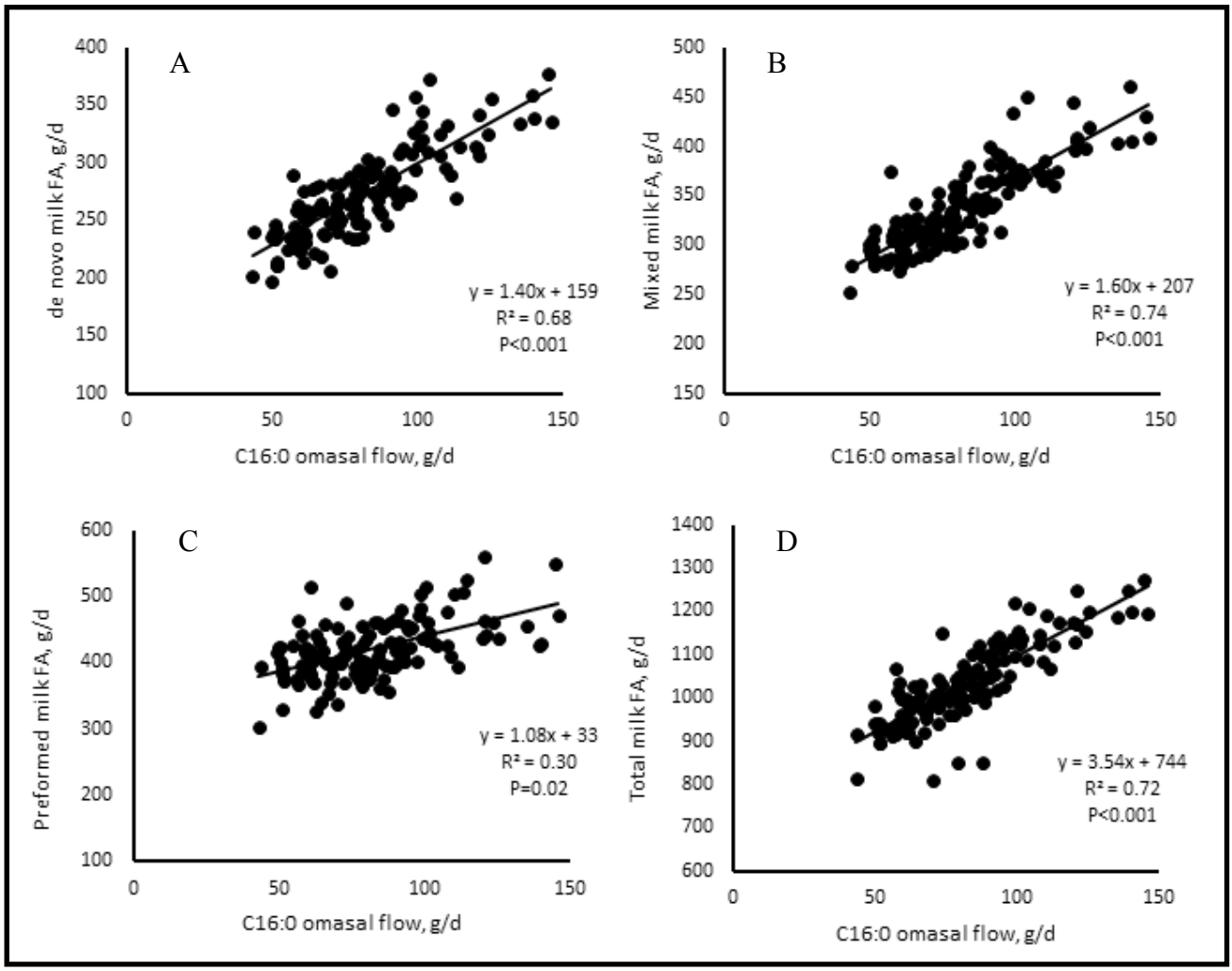

Figure 2. Relationship between C16:0 omasal flow and de novo milk FA (Panel A), mixed milk FA (Panel B), preformed milk FA (Panel C), and total milk FA (Panel D). Our analysis used individual observations (n=132) in lactating Nordic Red dairy cows from 9 Latin square or switch-back design studies. Mixed model regressions were developed between variables of interest taking into account experiment, period within experiment, and cow within experiment as random factors (de Souza et al., 2018a).

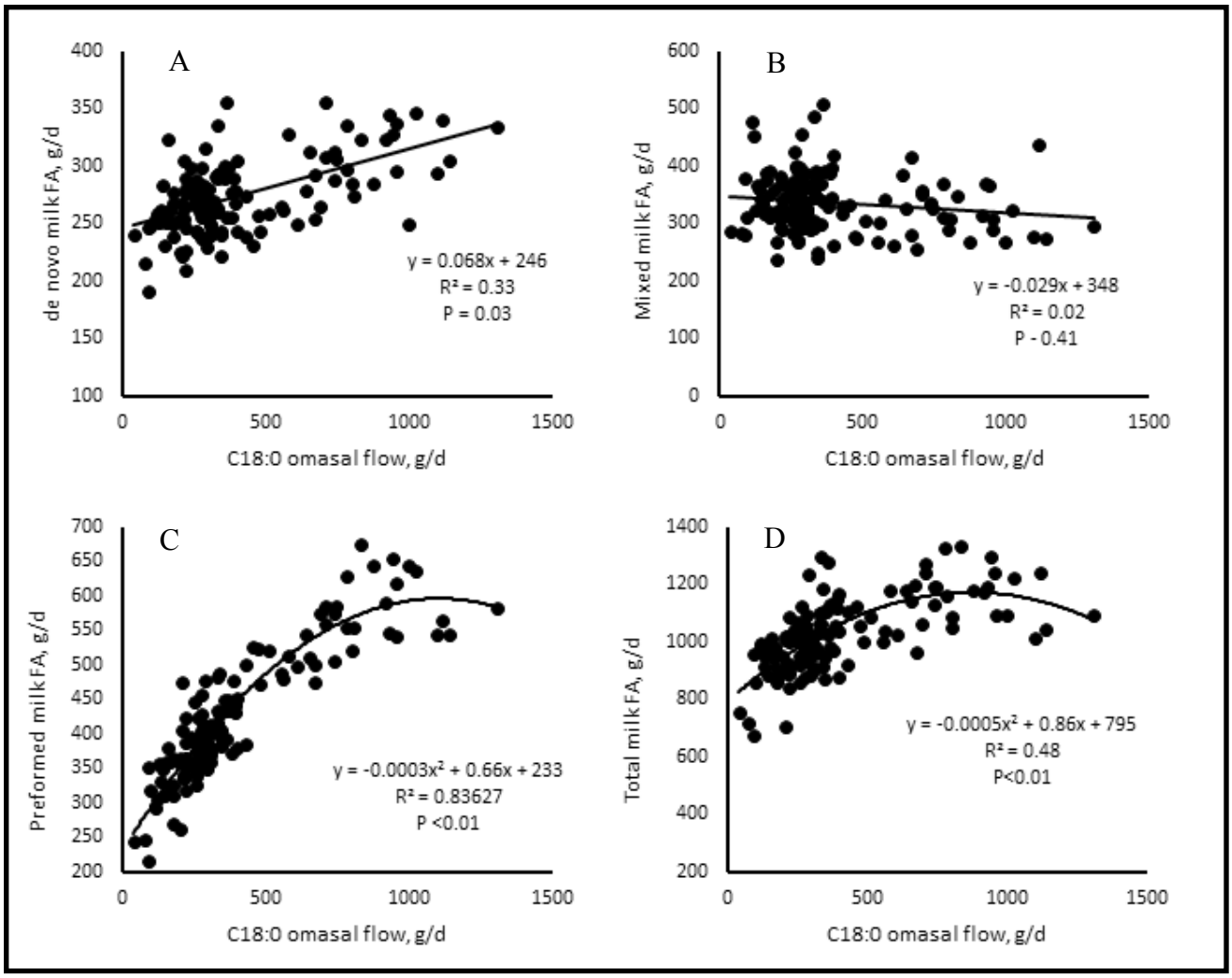

Figure 3. Relationship between C18:0 omasal flow and de novo milk FA (Panel A), mixed milk FA (Panel B), preformed milk FA (Panel C), and total milk FA (Panel D). Our analysis used individual observations (n=132) in lactating Nordic Red dairy cows from 9 Latin square or switch-back design studies. Mixed model regressions were developed between variables of interest taking into account experiment, period within experiment, and cow within experiment as random factors (de Souza et al., 2018a).

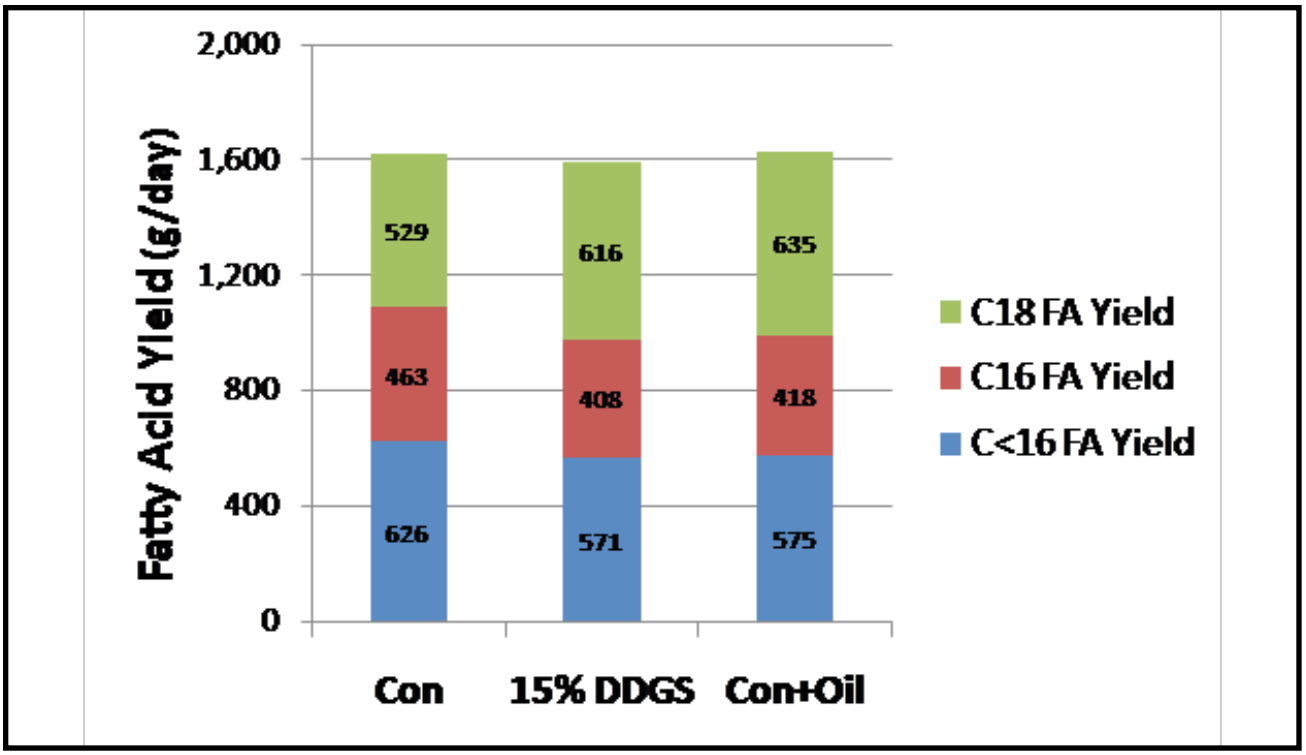

Figure 4. Effects of dry distillers grain (DDGS) and corn oil on the yield of de novo, mixed and performed milk FA in mid-lactation cows. Twenty multiparous lactating Holstein cows were assigned to a replicated, 5 × 5 Latin Square design with periods of 21 days (Leonardi et al., 2005). Figure from Lou Armentano (University of Wisconsin).

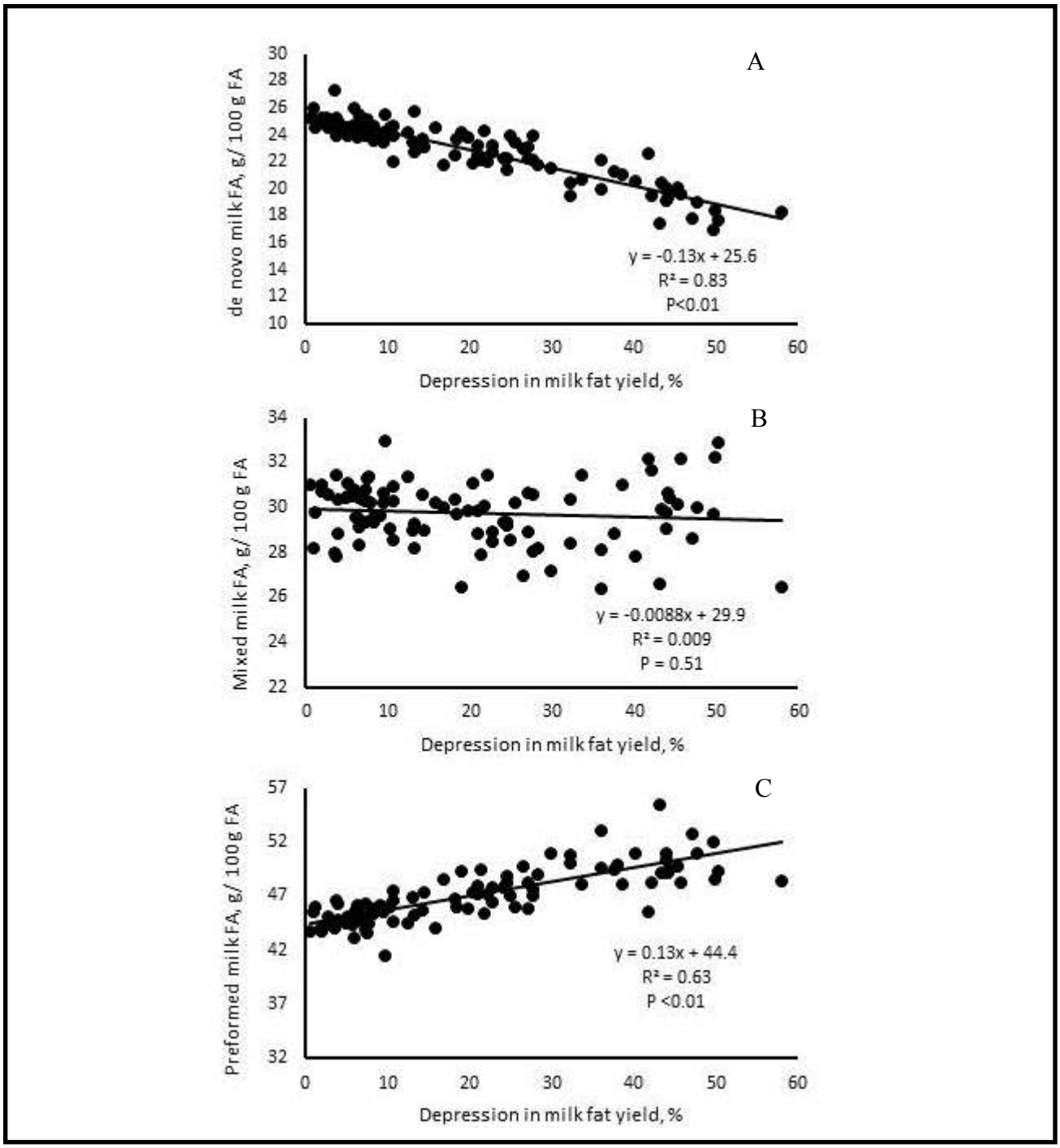

Figure 5. Relationship between the degree of diet-induced milk fat depression on the concentration of de novo milk FA (Panel A), mixed milk FA (Panel B), and preformed milk FA (Panel C). Our analysis used individual observations (n=134) in lactating dairy cows from 3 studies. Mixed model regressions were developed between variables of interest taking into account experiment, period within experiment, and cow within experiment as random factors (unpublished results).

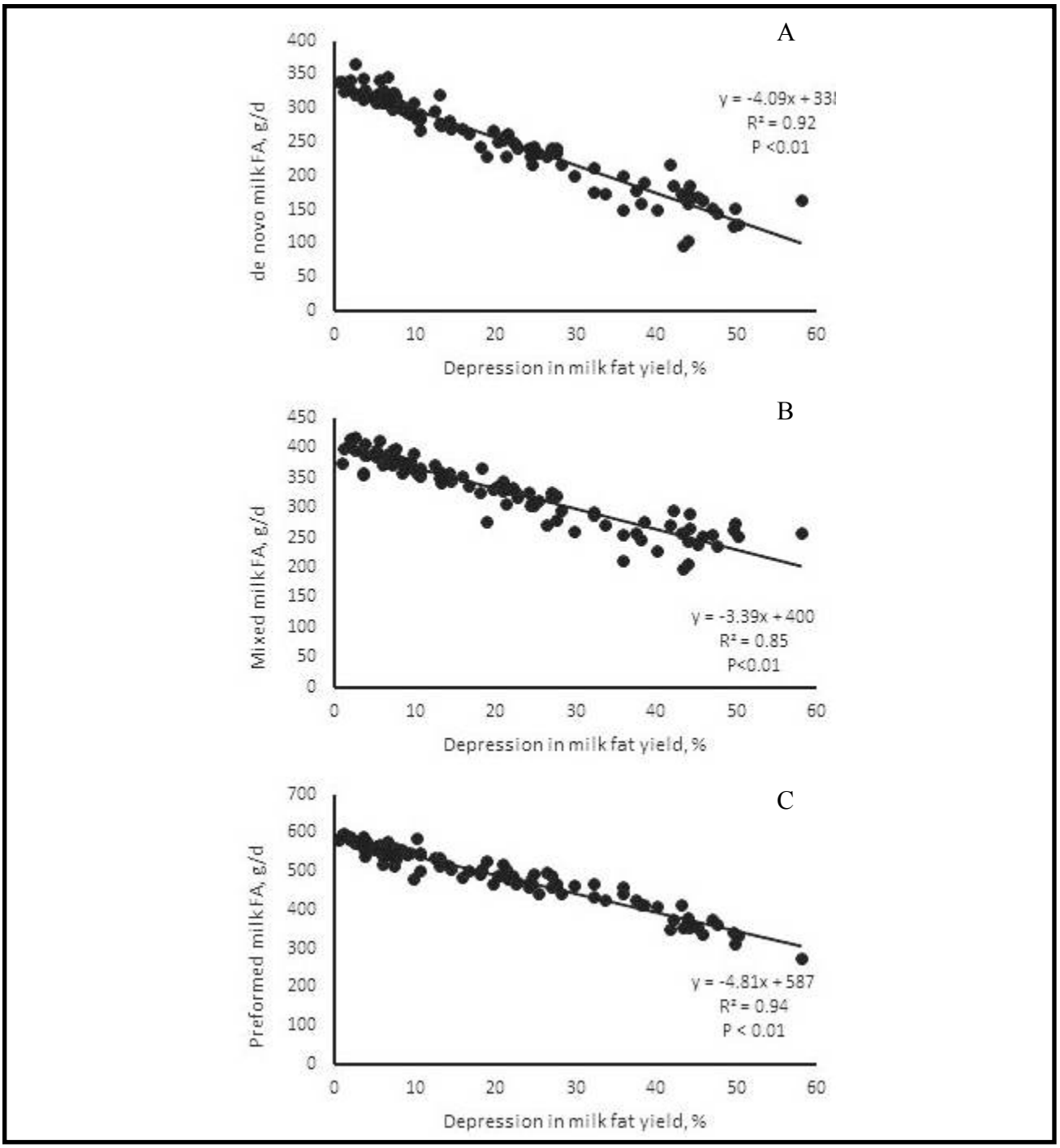

Figure 6. Relationship between the degree of diet-induced milk fat depression on the yield of de novo milk FA (Panel A), mixed milk FA (Panel B), and preformed milk FA (Panel C). Our analysis used individual observations (n=134) in lactating dairy cows from 3 studies. Mixed model regressions were developed between variables of interest taking into account experiment, period within experiment, and cow within experiment as random factors (unpublished results).

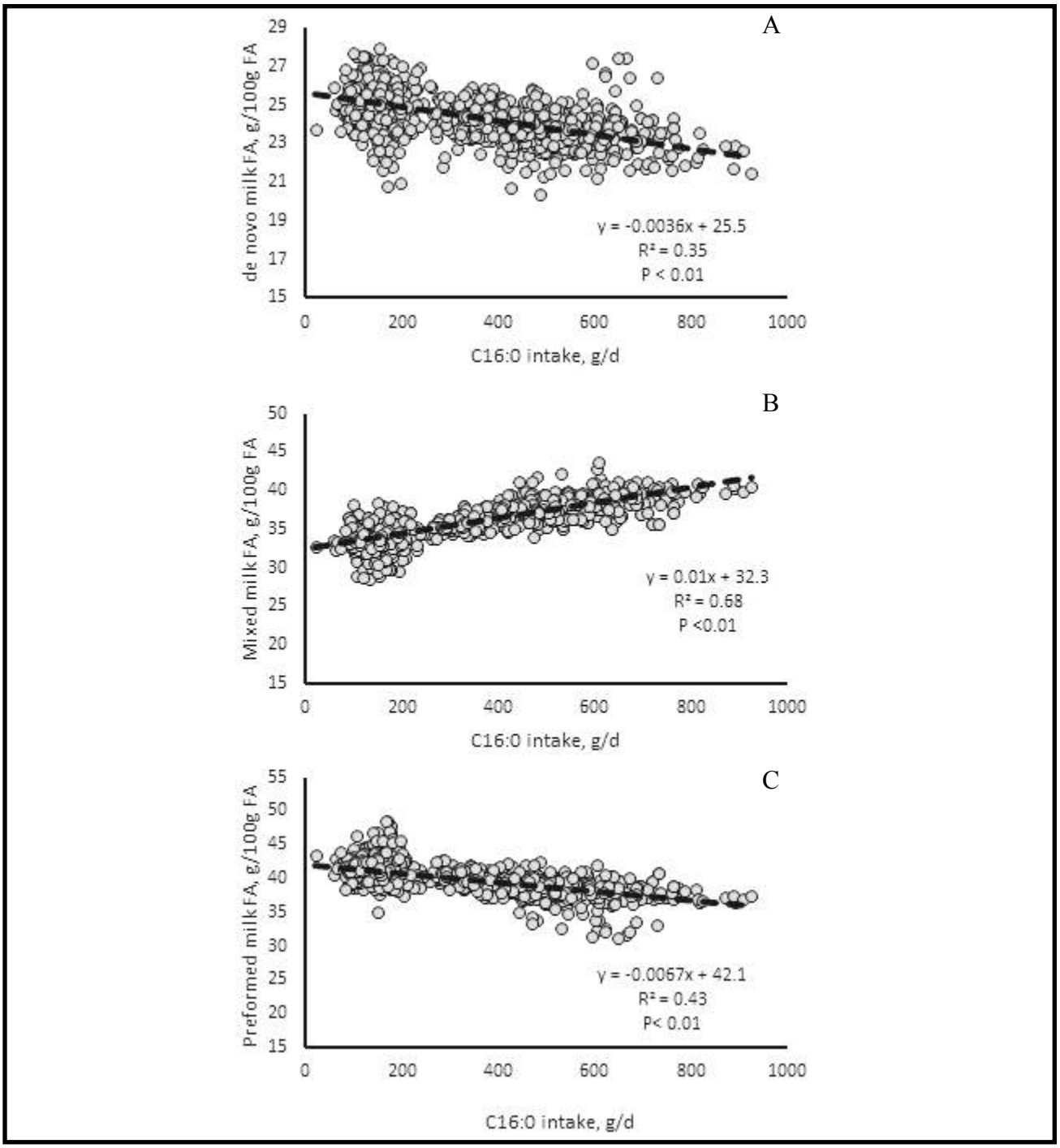

Figure 7. Relationship between C16:0 intake and the concentration of de novo milk FA (Panel A), mixed milk FA (Panel B), and preformed milk FA (Panel C). Our analysis used individual observations (n=1200) in lactating dairy cows from 13 studies. Mixed model regressions were developed between variables of interest taking into account experiment, period within experiment, and cow within experiment as random factors (unpublished results).

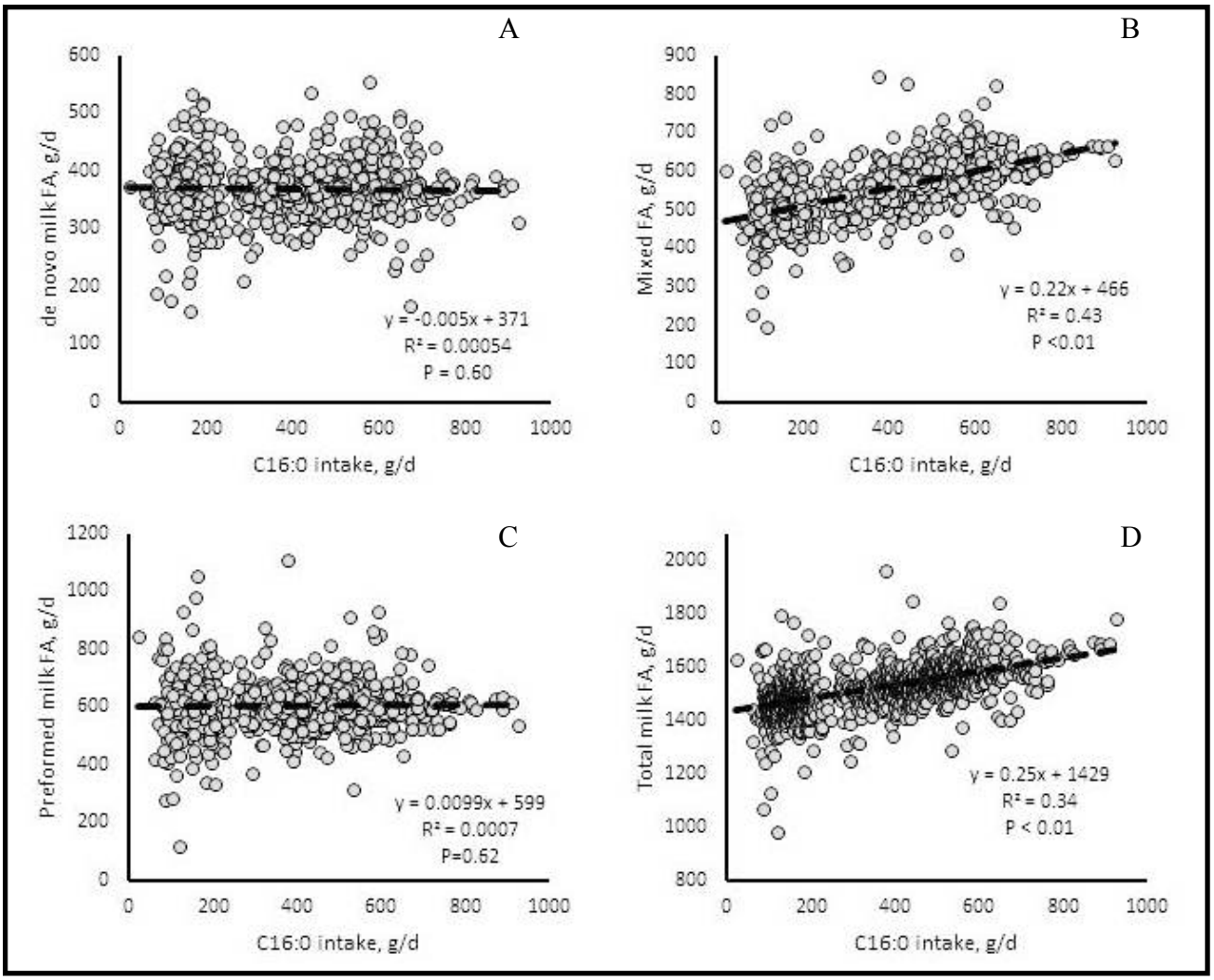

Figure 8. Relationship between C16:0 intake and the yield of de novo milk FA (Panel A), mixed milk FA (Panel B), preformed milk FA (Panel C), and total milk FA (Panel D). Our analysis used individual observations (n=1200) in lactating dairy cows from 13 studies. Mixed model regressions were developed between variables of interest taking into account experiment, period within experiment, and cow within experiment as random factors (unpublished results).