patient-oriented and epidemiological research

Weekday variation in triglyceride concentrations in 1.8 million blood samples[S]

Jörn Jaskolowski,[1,*] Christian Ritz,[*] Anders Sjödin,[*] Arne Astrup,[*] Pal B. Szecsi,[†] Steen Stender,[†] and Mads F. Hjorth[*]

Department of Nutrition, Exercise and Sports,* Faculty of Science, University of Copenhagen, Copenhagen, Denmark; and Department of Clinical Biochemistry,† Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

Abstract **Triglyceride (TG) concentration is used as a marker of cardiometabolic risk. However, diurnal and possibly weekday variation exists in TG concentrations. The objective of this work was to investigate weekday variation in TG concentrations among 1.8 million blood samples drawn between 2008 and 2015 from patients in the Capital region of Denmark. Plasma TG was extracted from a central clinical laboratory information system. Weekday variation was investigated by means of linear mixed models. In addition to the profound diurnal variation, the TG concentration was 4.5% lower on Fridays compared with Mondays ($P < 0.0001$). The variation persisted after multiple adjustments for confounders and was consistent across all sensitivity analyses. Out-patients and in-patients, respectively, had 5.0% and 1.9% lower TG concentrations on Fridays compared with Mondays (both $P < 0.0001$). The highest weekday variations in TG concentrations were recorded for out-patients between the ages of 9 and 26 years, with up to 20% higher values on Mondays compared with Fridays (all $P < 0.05$).** In conclusion, **TG concentrations were highest after the weekend and gradually declined during the week. We suggest that unhealthy food intake and reduced physical activity during the weekend increase TG concentrations which track into the week. This weekday variation may carry implications for public health and future research practice.**—Jaskolowski, J., C. Ritz, A. Sjödin, A. Astrup, P. B. Szecsi, S. Stender, and M. F. Hjorth. **Weekday variation in triglyceride concentrations in 1.8 million blood samples.** ***J. Lipid Res.*** **2017.** 58: **1204–1213.**

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A high concentration of plasma cholesterol (CH) has for years been considered a major risk factor for CVD (1, 2), and treatment has focused on lowering total non-HDL-CH. However, some observational studies and a meta-analysis have indicated that high plasma triacylglycerol/triglyceride (TG) concentrations may be an independent atherogenic risk factor. All interventional studies have been based upon fasting or postprandial TG concentrations, yet nonfasting TG concentrations seem to be more strongly associated with CVD than fasting TG concentrations (3, 4), as substantiated in a Mendelian randomization study (5).

An improved understanding of biological variation in clinically measured compounds in human material may be useful for many purposes in clinical chemistry (6). There may, however, be several sources of variation that contribute to the biological variation. Many compounds such as CH, TG, and other lipids have diurnal and seasonal variation, in addition to variation due to lifestyle behavior (7), but little is known about variation due to weekdays.

In a study with 807 8- to 11-year-old children, fasting TG concentrations were found to be 28% higher on Mondays compared with Fridays (8). However, to our knowledge, no study has investigated the weekday variations of TG concentrations in a large sample, including adults.

Therefore, the aim of this study was to investigate whether and to what extent TG concentrations vary according to the day of week using approximately 1.8 million unselected blood samples analyzed at hospitals in the Capital region in Denmark from 2008 through 2015. We hypothesized that TG concentrations would be higher on Mondays compared with Fridays.

MATERIALS AND METHODS

The present study was based on anonymized data extracted from a common clinical laboratory information system (Labka II; CSC, Tysons, VA). The database contains millions of stored test results from in- and out-patients in the Capital region of Denmark

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Abbreviations: ALAT, alanine transaminase; CH, cholesterol; CHO, carbohydrate; Hgb, hemoglobin; n-3 PUFA, long chain polyunsaturated omega-3 fatty acids; PA, physical activity; TG, triglyceride.

[1] To whom correspondence should be addressed.
e-mail: joern.jaskolowski@gmail.com

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with a population of about 1.8 million inhabitants. The samples were commissioned by general practitioners, specialists, and doctors during everyday life or hospitalization. Blood samples were obtained at various time points and for multiple reasons; thus, for routine checkups, suspicion of illness, hospital admission and readmission, during hospitalization, and before hospital discharge, they comprise measurements of various blood parameters from males and females of any age. The laboratory data were obtained from 13 hospital laboratories in the region with different instruments, varying both over time and by location. However, results were comparable due to common quality control systems and sample exchange. Most of the analyses were performed according to ISO-15189 accreditation.

The primary analytical sample comprised data from TG. Data of alanine transaminase (ALAT), hemoglobin (Hgb), and sodium were extracted to support the interpretation of the TG data. The test results for each blood sample were accompanied by information about the executive laboratory, date and time, patient-setting, fasting status, age, gender, and a unique subject identifier.

Analyses were mainly performed using Kone-lab, Espoo, Finland; Vitros 950/5.2 chemistry system (Johnson and Johnson, Rochester, NY); and Hitachi 912, Cobas Integra 400/800, Cobas Modular 6000/8000, Cobas Modular (Roche Diagnostics, Basel, Switzerland); Dimension Vista 1500 (Siemens Medical Solutions Diagnostics, Tarrytown, NY), and the Advia 120/2120 hematology system (Siemens); Sysmex XE, XI, or XN series (Sysmex, Kobe, Japan).

Colorimetric methods were used to measure TG in plasma according to the manufacturers' protocols. The relative expanded uncertainty for CH is approximately 10%, whereas for TGs it is approximately 22–23%. Plasma ALAT was measured according to the IFCC 2002 method, plasma sodium was measured with ion-selective electrodes, and blood Hgb with a non-cyanide method on automated hematology instruments.

Statistics

Weekday variation in TG, Hgb, ALAT, and sodium concentrations was described by means of linear mixed models; one model per outcome. Observations with missing data were excluded. Linear mixed models comprised fixed effects including gender, age-group (5 year intervals), fasting-status (fasting, nonfasting), hospitals, setting [out-patient, in-patient, in-between-patient (staying at the hospital during day time, but sleeping at home)], year, month, time of the day (hour), and subject-specific random effects. If appropriate, skewed variables were log-transformed and subsequently back-transformed. The majority of the TG and ALAT data was processed by this approach; whereas for Hgb and sodium, a log-transformation of the data was not required. Results were shown as mean concentrations with 95% CI, as estimated by the package, multcomp 1.4-4 (9). The difference between Monday and Friday was assessed through a pairwise comparison using a post hoc *t*-test. The same approach was used to test differences between weekdays and weekend days for hydration markers (Hgb and sodium). As hydration level was expected to be different on weekdays compared with weekend days, the difference between Monday and Friday for each marker was calculated. Sensitivity analysis for TG was performed in order to evaluate the robustness of the results in respect to various characteristics. Specifically, sensitivity analyses comprised aforementioned linear mixed models stratified according to samples $\leqslant$3.0 mmol/l ($\leqslant$266 mg/dl) and $\leqslant$1.7 mmol/l ($\leqslant$151 mg/dl), gender, patient-status, age (by each year), fasting-status, hospital, and sample time (year, month, hour). All the statistical analyses were conducted using R version 3.2.4 (10). Significance was declared whenever $P < 0.05$.

RESULTS

Characteristics of the 1,828,861 observations for TG, as well as for the observations for Hgb, sodium, and ALAT can be found in **Table 1**. The TG observations were obtained from a total of 633,123 subjects. A total of 80.6% of the TG samples were from out-patients, as were 40.1, 41.5, and 58.5% for sodium, Hgb, and ALAT, respectively. The overall proportion of TG concentrations $\geqslant$1.7 mmol/l ($\geqslant$151 mg/dl) was 32.7%; with 34.8, 34.0, 32.8, 31.3, and 29.7% for Monday through Friday, respectively. TG concentrations were 4.5% (4.3%, 4.7%; $P < 0.0001$) lower on Fridays compared with Mondays when using mixed models (**Table 2**). Furthermore, negligible differences were observed between Monday and Friday for Hgb and sodium concentrations (both $P < 0.0001$), whereas no difference was observed for ALAT ($P = 0.11$). Concentrations of Hgb on all of the weekdays were systematically higher compared with weekend days (all $P < 0.0001$), whereas this was the opposite for ALAT (all $P < 0.0001$).

Weekday variation in TG concentrations remained after stratifying on age (**Fig. 1**, supplemental Table 1), gender, truncation of values, fasting status, setting, hospital, year, and month (**Table 3**). The variation from Monday to Friday was roughly 10% for 14–26 years of age, followed by gradually decreasing variations of about 4% around age 65. The decline in variation continued, reaching nonsignificance at the age of 80 years. Only 1.4% of the <1-year-old infants and 31% of the children between 1 and 9 years were out-patients. The proportion of out-patients exceeded 50% by the age of 9 years and increased linearly to 84% until the age of 74 years (data not shown). Out-patients had a Monday to Friday difference of −5.0%, while in-patients had a difference of −1.9% (both $P < 0.0001$). Out-patients had systematically larger weekday variation in each of the age groups, as shown in Fig. 1. The highest variations were recorded for out-patients between 9 and 26 years of age, with up to 20% higher values on Monday compared with Friday (all $P < 0.05$). The differences were −5.5% and −4.4% in fasting and nonfasting samples (both $P < 0.0001$), respectively. In view of the different seasons, the lowest Monday to Friday variations were observed in April and July (both −3.7%, $P < 0.0001$).

On all weekdays, TG concentrations were lowest around 7:00 AM, ranging from 1.61 mmol/l (143 mg/dl) on Mondays to 1.52 mmol/l (135 mg/dl) on Fridays. The time trends for out-patients were in accordance with the overall data (**Fig. 2**). Patterns between 7:00 AM and 2:00 PM on each weekday were comparable; however with each subsequent day of the week, the TG concentrations declined. On average, the TG concentrations reached their peak at 2:00 PM each weekday with 23.3, 22.3, 24.3, 22.1, and 27.4% higher concentrations compared with concentrations at 7:00 AM on Monday to Friday, respectively. The highest number of observations was recorded at 7:00 AM with more than 50,000 observations on each weekday. After 1:00 PM the number of observations dropped rapidly to less than 700 observations at 2:00 PM on Friday. The weekday variation for plasma total-CH,

TABLE 1. Characteristics of the study population according to TG, Hgb, sodium, and ALAT status

Characteristics	TG	Hgb	Sodium	ALAT
Observations (n)	1,828,861	3,000,000	1,544,204	3,000,000
Gender (% female)	48.2	51.3	50.1	52.7
Age (years)	63 (36–80)	64 (29–84)	67 (33–85)	61 (28–81)
Setting (%)				
Out-patient	80.6	41.5	40.1	58.5
In-patient	18.0	56.9	58.6	39.8
In-between-patient	1.4	1.6	1.3	1.7
Fasting-status (%)				
Non-fasting	87.1	100	100	100
Fasting	12.9	—	—	—
Day (%)				
Monday	21.0	19.3	19.3	20.7
Tuesday	22.3	18.4	18.4	19.9
Wednesday	20.0	17.8	17.5	18.7
Thursday	20.2	17.3	16.8	18.4
Friday	13.7	14.7	14.7	14.2
Saturday	1.4	6.3	6.6	4.0
Sunday	1.4	6.3	6.6	4.1
Year (%)				
2008	1.3	1.2	—	0.9
2009	8.7	8.2	—	7.2
2010	11.2	10.4	—	9.7
2011	13.5	13.6	—	12.8
2012	14.8	15.5	—	15.2
2013	15.9	16.2	—	16.9
2014	17.0	17.3	100.0	18.4
2015	17.6	17.5	—	18.9

Data are expressed as n, median (10th to 90th percentile), or proportion.

LDL-CH, and HDL-CH were all less than 1% (supplemental Table 2).

DISCUSSION

In support of the hypothesis, TG varied according to weekdays, with higher concentrations on Mondays compared with Fridays. The overall observed variation of 4.5% between Mondays and Fridays in TG concentrations is based on more than 1.8 million samples and persisted after multiple adjustments. The phenomenon exists across gender, age, hospital, fasting state of the sample, year, month, hour of the day, and after truncation of abnormal values. The variation between Monday and Friday was negligible for total-CH, LDL-CH, HDL-CH, Hgb, and sodium, as well as not present for ALAT; this speaks against an effect on TG concentrations caused by variation in hydration level and suggests that it is not caused by high alcohol intake. Anticipating that the sampling on weekends is done more frequently on patients with more serious illnesses, results from weekend days need to be interpreted with caution.

Of particular interest, out-patients showed higher weekday variation than in-patients and the weekday variation was highest in adolescence with gradually decreasing differences by age. The explanation for this phenomenon could be that lifestyle factors are less controlled in out-patients that probably continue their usual diet, drinking, and exercise habits compared with the more restricted hospital environment.

The average alcohol consumption among Danes is higher from Friday to Sunday compared with Monday through Thursday (11) and several observational studies have shown an association between alcohol intake and increased TG concentrations (12). Although acute intake of alcohol elevates TG concentrations by roughly 15% (13) to 60% (14) 1 and 3 h after consumption of 30 g of alcohol together with a meal, TG concentration returns to baseline after an overnight fast. In support of this, the present study was unable to detect weekday variation in 3 million ALAT observations. Alcohol intake and ALAT have been linearly associated in men (15); however, the role of ALAT as a sensitive marker for acute alcohol intake is questionable, as it has a long half-life time and fluctuates within and between days (16, 17). Therefore, we cannot exclude alcohol as a mediator of the observed weekday variation in TG. Against the hypothesis of an alcohol-mediated effect is the large TG variation in 9- to 14-year-old out-patient children in the present study, and the 28% higher TG concentrations on Mondays compared with Fridays in 8- to 11-year-old healthy children found in another Danish observational study (8). We speculate that these age groups are unlikely to consume any alcohol and our observed weekday variation in TG concentrations is, therefore, most likely not related to alcohol intake.

Previous studies suggest that carbohydrate (CHO)-rich diets induce hypertriglyceridemia (18, 19), as shown for both fructose and glucose under controlled conditions (20). Switching from a high-fat (70%) diet to a high-CHO (75%) diet, TG concentrations have been found to rise significantly within 1 week and reach their peak after 4 weeks. After shifting back, TG concentrations declined gradually over a course of weeks with the largest changes in the first week (19). In another study of 14 healthy postmenopausal women, the habitual diet was changed gradually to reduce dietary fat intake and increase CHO intake over a period of 3 months. In response, the TG concentrations increased from 2.1 mmol/l (186 mg/dl) to 2.5 mmol/l (221 mg/dl) between the first and the second half of the study with the diets comprising 60% CHO and 67% CHO, respectively (18). Fat-rich meals also have the potential to induce hypertriglyceridemia (21, 22). It has been shown that meals containing 70 g of fat raised TG concentrations by 70% with its peak at 3 h subsequent to consumption (22). Long-chain polyunsaturated omega-3 fatty acids (n-3 PUFAs), particularly EPA and DHA, are known to lower fasting TG concentrations by 20–40%, depending on the n-3 dose and the TG baseline value (23, 24). Even though it is evident that n-3 PUFAs reduce TG concentrations, intervention periods are commonly greater than 4 weeks with average intakes of 3–4 g of EPA and DHA daily (23, 24). Acute effects of n-3 PUFA have only been recorded with a single dose of 20 g fish oil (68% n-3 PUFA), which reduced TG concentrations by 33% 14 h after the ingestion (25). However, daily concentrations above 2 g are difficult to obtain from the diet (26).

Previous literature shows that energy intake above the individual requirement results in the overproduction of VLDL in the liver and consequently increases TG concentrations (27–29). Current research suggests that the effect of positive energy balance on TG metabolism is determined

TABLE 2. Weekday variation in TG, Hgb, sodium, and ALAT status

	Monday		Tuesday		Wednesday		Thursday		Friday		Saturday		Sunday		Diff. (%)	
	n		n		n		n		n		n		n			
	Mean (95% CI)		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)			*P* for Diff.
TG (mmol/l)	383,523		407,973		366,510		368,983		249,996		25,926		25,950		−4.5 (−4.7;−4.3)	
	1.68 (1.68;1.69)		1.68 (1.68;1.68)		1.65 (1.65;1.65)		1.63 (1.62;1.63)		1.61 (1.61;1.61)		1.63 (1.62;1.63)		1.62 (1.61;1.63)			<0.0001
Hgb (mmol/l)	577,715		551,585		534,626		519,079		440,553		187,708		188,734		−0.4 (−0.4;−0.3)	
	7.78 (7.78;7.78)		7.78 (7.78;7.78)		7.76 (7.76;7.77)		7.76 (7.76;7.76)		7.75 (7.75;7.76)		7.66 (7.65;7.66)		7.68 (7.65;7.66)			<0.0001
Sodium (mmol/l)	298,186		284,574		269,718		259,389		227,653		102,178		102,506		−0.04 (−0.06;−0.03)	
	138.89		138.83		138.85		138.89		138.84		138.81		138.86			<0.0001
	(138.88;138.91)		(138.81;138.84)		(138.83;138.87)		(138.87;138.91)		(138.82;138.86)		(138.79;138.84)		(138.84;138.89)			
ALAT (U/l)	620,034		596,627		562,317		552,747		425,284		120,421		122,570		0.1 (0.0;0.3)	
	36.25 (36.11;36.38)		36.18 (36.12;36.24)		36.33 (36.27;36.39)		36.42 (36.35;36.48)		36.30 (36.23;36.37)		36.88 (36.77;36.98)		36.77 (36.66;36.88)		>0.11	

Data are presented as mean and 95% CI per day using a linear mixed model adjusted for gender, age-group (5 year intervals), fasting-status (fasting, nonfasting), hospitals, setting (out-patient, in-patient, in-between-patient), year, month, time of the day (hour) as fixed effects. and subject as random effect. The mean and 95% CI are expressed as mmol/l. TG: 1 mmol/l is equivalent to 88.57 mg/dl; Hgb: 1 mmol/l is equivalent to 1.61 g/dl; sodium: 1 mmol/l is equivalent to 2.3 mg/dl. *P* for Diff. between Monday and Friday was obtained using pairwise comparisons. Diff., difference between Monday and Friday (negative percentage indicates a higher value on Monday compared with Friday); n, number of observations.

by the macronutrient consumed in excess. Overfeeding of CHO for a period of 4–7 days increased the concentration of TGs up to 79% (27–30), whereas overconsumption of fat lead to either a reduction (29, 31) or no changes in TG concentrations (32). In contrast, dietary energy restriction appears to reduce TG concentrations (33–35). Even 1 day of moderate energy deficit (2 MJ) reduced fasting and postprandial TG concentrations by 15% and 12%, respectively (33).

Multiple studies have found exercise to reduce fasting and postprandial TG concentrations (36–38). Exercise-induced effects on TG concentrations have been documented as a 12 h delay subsequent to a bout of exercise (33, 39) and the TG concentrations will remain lower than the baseline values for about 2–3 days, after which the effect fades (40–44). Various studies applied altered exercise intensity and time to determine an energy expenditure threshold of 2–3 MJ to induce a TG lowering effect (38, 45–47). A session of exercise equal to approximately 3 MJ expended energy reduces plasma TG concentrations the following day in the postprandial state by 17–33% (45–49) and in the fasting state by 15–25% (38, 45, 46, 48). Therefore, the major cause of the TG-lowering effect during weekdays is plausibly energy expenditure. Furthermore, evidence emerges that the energy expenditure threshold can also be overcome by a combination of mild dietary restriction and light exercise (50).

A recent survey found Danish children to have about 10–12% higher energy consumption on Fridays and weekends compared with the remaining days of the week with more added sugar comprising some of this difference (51). Danish adults have also been reported to consume 13% more energy during weekends with a higher sugar intake (11). There is no indication that additional exercise compensates for the excess energy intake on weekend days, considering that children are less physically active and more sedentary on these days (52). Based on these results, energy imbalance may be speculated to be a rationale for the observed Monday to Friday variation. In support of this energy imbalance theory between weekdays and weekends, higher leptin and lower ghrelin have been found in children on Mondays compared with Fridays with a gradual decline from Monday to Friday (8). In the present study, Monday to Friday variations were largest in late childhood until young adulthood and gradually decreased with age. The dietary and physical activity (PA) patterns for children are highly structured due to school during the week, whereas the patterns for adults have larger variability and are likely to change during different cycles of life, e.g., moving out, parenthood, or retirement, therefore patterns are not as generalizable as those of children. Hence, the complexity of adult PA behavior may also be speculated to reflect the lower Monday to Friday variation compared with children.

In-patients have to adapt to hospital procedures, such as meal choice and PA independent of weekday, whereas out-patients are autonomous in their eating and PA behavior. The rather small weekday variation for in-patients and fairly large weekday variation for out-patients therefore

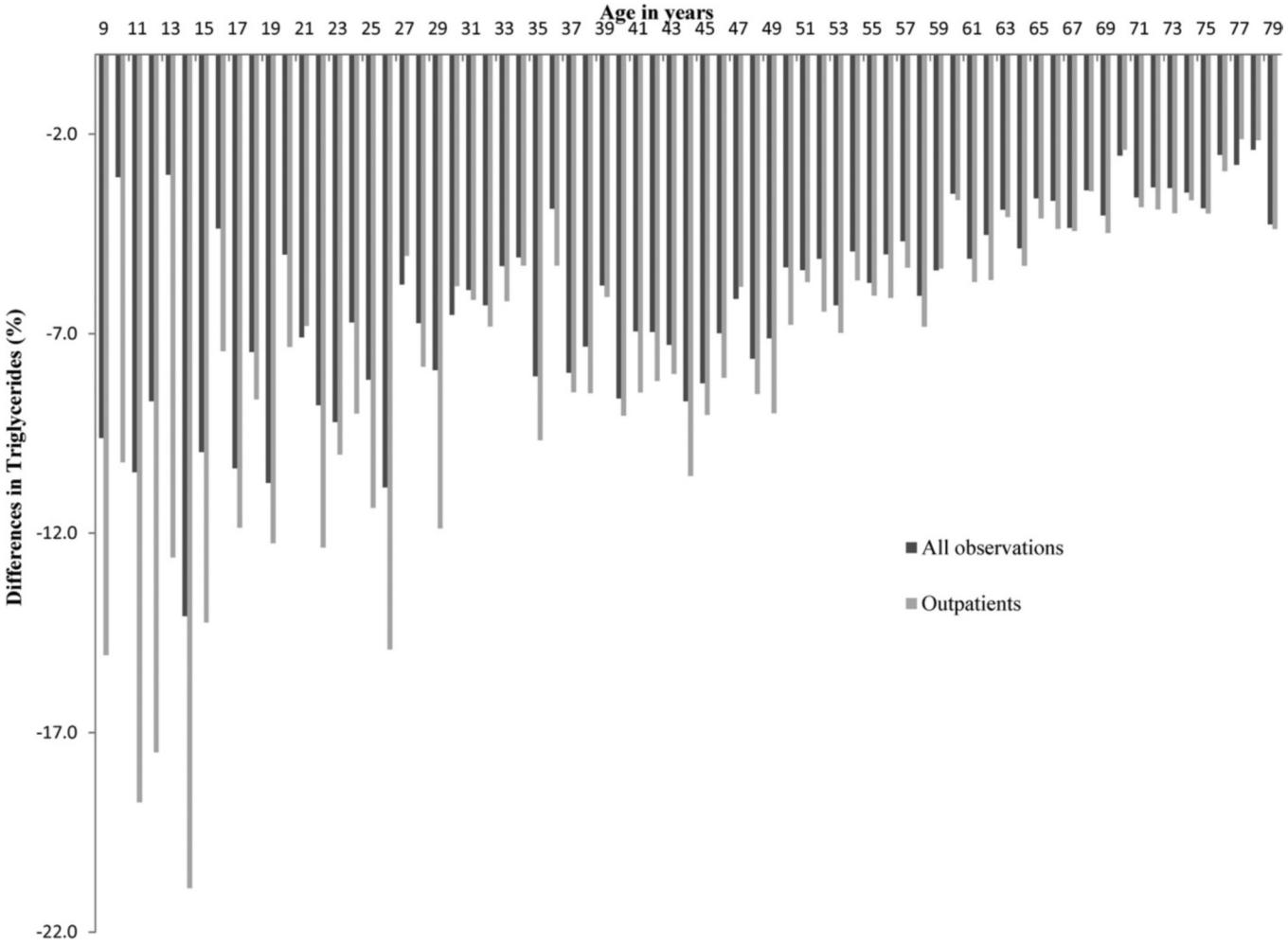

Fig. 1. Difference (percent) in TG concentrations from Monday to Friday by age (years) for all observations and out-patients with more than 100 observations on each day. Data are presented as the percentage difference from Monday and are based on means using a linear mixed model with gender, fasting-status (fasting, nonfasting), hospitals, year, month, and time of the day (hour) as fixed effects, and subject as random effect. Additionally "All observations" are adjusted for setting (out-patient, in-patient, in-between-patient). Number of observations in out-patients ranging from 106 to 727 on each Monday or Friday during adolescence followed by gradually increasing numbers up to age 68 (n > 5,812) then decreasing gradually (n > 2,574 at age 79).

may support that eating and PA behavior are among the main drivers of this weekday variation in TG. As it was recently found that objectively measured PA of children varies considerably more between weekdays and weekend days during winter compared with spring (52), this behavior theory may be further supported by our weekday variation being largest in November, February, and March and lowest during April, May, and July.

TG concentrations fluctuate in response to dietary intake. Most individuals eat regularly throughout the day, hence TG concentrations are very dynamic and lowest concentrations are usually measured in the morning after overnight fasting. It has been shown that TG concentrations increase up to 20% and remain elevated up to 6 h subsequently to the last meal (53, 54), which has been acknowledged (55), but disregarded, due to clinical unimportance and practicalities in clinical practice (56). The present study was able to confirm this daily variation in TG with differences ranging from 22% to 27% between 7:00 AM and 2:00 PM on each weekday. Fluctuations in CH concentrations have been suggested to range between 5% and 10% (57) and are to a lesser extent affected by alcohol, total energy intake, CHO-rich diets, and exercise (14, 48, 49, 58). The present study observed only minor weekly variation for CH concentrations.

Moreover, it has been suggested that the occurrence of acute myocardial infarction, sudden death, and cardiac arrest is higher on Monday compared with the rest of the week (59–62). The Monday phenomenon has also been published for onset of ischemic stroke (63).

Strengths of the present study include the large amount of samples representing a wide range of subjects across all ages from 13 different hospitals and making subgroup analysis possible without limiting power. Furthermore, Hgb and sodium measurements were used to investigate the potential differences in hydration status. Multiple covariates were used to adjust the analyses and reduce confounding. TG measurements performed at the hospitals are in most cases not affected by the potential disease or treatment of the patients. Results for out-patients, especially, may

TABLE 3. Weekday variation for TGs in different strata of the population

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Diff. (%)
	n	n	n	n	n	n	n	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*P* for Diff.
Gender								
Female	183,405	196,780	177,491	178,531	120,598	12,065	12,094	−4.4 (−4.6;−4.2)
	1.57 (1.56;1.57)	1.56 (1.55;1.56)	1.53 (1.53;1.53)	1.51 (1.51;1.51)	1.50 (1.49;1.50)	1.51 (1.50;1.52)	1.51 (1.50;1.52)	<0.0001
Male	200,118	211,193	189,019	190,452	129,398	13,861	13,856	−4.6 (−4.9;−4.4)
	1.79 (1.79;1.80)	1.79 (1.79;1.79)	1.76 (1.75;1.76)	1.73 (1.72;1.73)	1.71 (1.71;1.71)	1.73 (1.72;1.74)	1.86 (1.72;1.74)	<0.0001
Truncation								
TG ⩽ 3.0 (mmol/l)	349,511	373,006	336,157	340,353	231,547	23,487	23,545	−4.4 (−4.5;−4.2)
	1.40 (1.40;1.40)	1.39 (1.39;1.40)	1.37 (1.37;1.37)	1.35 (1.35;1.35)	1.34 (1.33;1.34)	1.34 (1.33;1.34)	1.34 (1.33;1.34)	<0.0001
TG ⩽ 1.7 (mmol/l)	252,066	271,436	248,013	255,179	176,886	17,708	17,714	−3.4 (−3.6;−3.3)
	1.09 (1.09;1.09)	1.09 (1.09;1.09)	1.07 (1.07;1.08)	1.06 (1.06;1.06)	1.05 (1.05;1.05)	1.05 (1.05;1.05)	1.05 (1.05;1.05)	<0.0001
Setting								
Out-patient	315,205	345,408	307,861	306,749	197,633	614	1402	−5.0 (−5.2;−4.8)
	1.68 (1.67;1.68)	1.67 (1.67;1.68)	1.64 (1.63;1.64)	1.61 (1.61;1.62)	1.60 (1.59;1.60)	1.57 (1.52;1.62)	1.67 (1.64;1.70)	<0.0001
In-patient	62,480	57,394	53,671	57,109	48,764	25,267	24,419	−1.9 (−2.4;−1.4)
	1.69 (1.68;1.70)	1.69 (1.69;1.70)	1.68 (1.67;1.69)	1.67 (1.66;1.68)	1.66 (1.65;1.67)	1.66 (1.65;1.67)	1.66 (1.65;1.67)	<0.0001
In-between-patient	5,838	5,171	4,978	5,125	3,599	45	129	−2.7 (−4.3;−1.2)
	1.87 (1.83;1.91)	1.85 (1.83;1.88)	1.85 (1.82;1.87)	1.83 (1.80;1.86)	1.82 (1.79;1.85)	1.76 (1.55;1.96)	1.79 (1.67;1.91)	0.0006
Fasting-status								
Non-fasting	334,531	354,191	320,213	318,156	216,475	24,911	24,947	−4.4 (−4.6;−4.2)
	1.70 (1.70;1.71)	1.69 (1.69;1.70)	1.66 (1.66;1.67)	1.64 (1.64;1.65)	1.63 (1.62;1.63)	1.64 (1.63;1.65)	1.64 (1.63;1.65)	<0.0001
Fasting	48,992	53,782	46,297	50,827	33,521	1,015	1,003	−5.5 (−6.0;−5.0)
	1.58 (1.57;1.59)	1.58 (1.57;1.58)	1.54 (1.53;1.55)	1.51 (1.50;1.52)	1.49 (1.48;1.50)	1.50 (1.46;1.54)	1.54 (1.50;1.58)	<0.0001
Hospitals								
A	22,163	21,104	18,621	22,781	13,350	1,212	1,533	−2.8 (−3.5;−2.0)
	1.80 (1.78;1.82)	1.79 (1.78;1.80)	1.78 (1.76;1.79)	1.75 (1.74;1.77)	1.75 (1.74;1.77)	1.75 (1.71;1.79)	1.71 (1.67;1.74)	<0.0001
B	32,476	30,764	29,007	28,294	20,499	4,756	4,542	−3.8 (−4.6;−3.0)
	1.82 (1.81;1.84)	1.82 (1.81;1.83)	1.80 (1.79;1.81)	1.78 (1.77;1.79)	1.76 (1.74;1.77)	1.73 (1.70;1.75)	1.76 (1.74;1.79)	<0.0001
C	30,861	30,229	28,924	29,337	24,256	4,122	4,114	−3.4 (−4.1;−2.7)
	1.67 (1.66;1.69)	1.67 (1.66;1.68)	1.65 (1.64;1.66)	1.62 (1.61;1.63)	1.61 (1.60;1.63)	1.64 (1.61;1.66)	1.63 (1.60;1.65)	<0.0001
D	20,927	21,067	17,105	22,656	15,181	611	515	−4.7 (−5.4;−4.0)
	1.55 (1.53;1.57)	1.55 (1.54;1.56)	1.51 (1.50;1.52)	1.49 (1.48;1.50)	1.48 (1.46;1.49)	1.50 (1.45;1.54)	1.55 (1.50;1.60)	<0.0001
E	9,286	10,489	9,245	9,014	8,550	1,387	1,213	−1.4 (−2.5;−0.3)
	1.76 (1.72;1.80)	1.78 (1.76;1.80)	1.75 (1.73;1.77)	1.74 (1.72;1.76)	1.74 (1.72;1.76)	1.73 (1.69;1.77)	1.72 (1.67;1.76)	0.0158
F	123,210	138,333	120,704	120,035	79,826	2,200	2,255	−5.7 (−6.0;−5.4)
	1.68 (1.67;1.68)	1.67 (1.67;1.68)	1.63 (1.63;1.63)	1.61 (1.60;1.61)	1.58 (1.58;1.59)	1.62 (1.59;1.64)	1.64 (1.62;1.67)	<0.0001
G	364	1,882	687	1,717	393	0	1	−0.9 (−6.0;4.2)
	2.06 (1.87;2.24)	2.14 (2.04;2.24)	1.97 (1.87;2.06)	2.09 (1.99;2.19)	2.04 (1.93;2.14)	0 (0;0)	3.79 (1.50;6.07)	0.7369
H	33,101	36,172	34,041	32,155	19,911	534	538	−5.7 (−6.3;−5.1)
	1.57 (1.55;1.58)	1.55 (1.55;1.56)	1.53 (1.52;1.54)	1.50 (1.49;1.51)	1.48 (1.47;1.49)	1.57 (1.52;1.61)	1.53 (1.49;1.58)	<0.0001
I	29,444	37,890	32,893	32,164	19,567	609	636	−5.3 (−5.9;−4.7)
	1.63 (1.62;1.65)	1.63 (1.62;1.64)	1.59 (1.58;1.60)	1.56 (1.55;1.57)	1.55 (1.54;1.56)	1.62 (1.58;1.67)	1.57 (1.53;1.62)	<0.0001
J	26,391	27,745	25,544	22,998	7,934	494	522	−3.7 (−4.5;−2.9)
	1.69 (1.67;1.70)	1.68 (1.67;1.69)	1.64 (1.63;1.65)	1.63 (1.62;1.64)	1.62 (1.61;1.64)	1.64 (1.59;1.69)	1.63 (1.57;1.68)	<0.0001
K	12,475	12,442	11,303	11,206	9,368	2,214	2,299	−1.6 (−2.7;−0.6)
	1.65 (1.63;1.67)	1.66 (1.65;1.68)	1.63 (1.62;1.65)	1.63 (1.61;1.64)	1.62 (1.61;1.64)	1.62 (1.59;1.65)	1.62 (1.59;1.65)	0.0024
L	25,478	23,233	21,937	22,374	18,200	4,973	5,221	−2.0 (−2.7;−1.3)
	1.74 (1.73;1.76)	1.73 (1.72;1.75)	1.71 (1.70;1.73)	1.70 (1.69;1.72)	1.71 (1.69;1.72)	1.72 (1.70;1.74)	1.70 (1.68;1.72)	<0.0001
M	17,347	16,623	16,499	14,252	12,961	2,814	2,561	−3.1 (−3.9;−2.2)
	1.73 (1.72;1.75)	1.73 (1.72;1.75)	1.70 (1.68;1.71)	1.68 (1.67;1.70)	1.67 (1.65;1.68)	1.66 (1.63;1.69)	1.66 (1.63;1.69)	<0.0001

TABLE 3. Continued.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Diff. (%)
	n	n	n	n	n	n	n	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*P* for Diff.
Year								
2008	4,922	5,514	4,535	4,692	3,583	244	223	−6.4 (−8.5;−4.3)
	1.61 (1.57;1.64)	1.60 (1.57;1.63)	1.55 (1.52;1.58)	1.55 (1.51;1.58)	1.50 (1.47;1.54)	1.52 (1.42;1.62)	1.54 (1.43;1.64)	<0.0001
2009	31,448	36,990	32,027	33,501	22,195	1,571	1,638	−5.4 (−6.1;−4.7)
	1.60 (1.61;1.65)	1.63 (1.62;1.64)	1.60 (1.59;1.61)	1.57 (1.56;1.58)	1.54 (1.53;1.55)	1.55 (1.52;1.59)	1.56 (1.53;1.60)	<0.0001
2010	41,332	47,546	41,457	42,446	27,420	2,161	2,226	−5.5 (−6.2;−4.9)
	1.63 (1.62;1.64)	1.63 (1.62;1.64)	1.59 (1.58;1.60)	1.56 (1.55;1.57)	1.54 (1.53;1.55)	1.59 (1.56;1.62)	1.59 (1.57;1.62)	<0.0001
2011	50,979	55,648	50,103	50,493	33,116	3,669	3,524	−5.4 (−6.0;−4.8)
	1.66 (1.64;1.66)	1.66 (1.65;1.66)	1.63 (1.62;1.64)	1.60 (1.59;1.61)	1.57 (1.56;1.58)	1.61 (1.59;1.63)	1.62 (1.60;1.64)	<0.0001
2012	57,061	58,893	54,428	55,668	36,475	4,461	4,521	−4.5 (−5.1;−4.0)
	1.65 (1.64;1.66)	1.65 (1.64;1.65)	1.62 (1.59;1.61)	1.60 (1.59;1.61)	1.58 (1.57;1.58)	1.60 (1.58;1.62)	1.58 (1.56;1.61)	<0.0001
2013	62,444	62,950	56,580	59,321	40,083	4,491	4,431	−4.7 (−5.2;−4.1)
	1.69 (1.68;1.70)	1.68 (1.67;1.69)	1.65 (1.64;1.66)	1.63 (1.62;1.64)	1.61 (1.60;1.62)	1.61 (1.59;1.63)	1.62 (1.59;1.64)	<0.0001
2014	66,555	68,907	62,229	59,818	43,483	4,570	4,688	−4.3 (−4.8;−3.8)
	1.73 (1.72;1.74)	1.73 (1.72;1.74)	1.69 (1.69;1.70)	1.68 (1.67;1.69)	1.66 (1.65;1.67)	1.69 (1.67;1.71)	1.65 (1.63;1.67)	<0.0001
2015	68,782	71,525	65,151	63,044	43,641	4,759	4,699	−4.3 (−4.8;−3.9)
	1.74 (1.73;1.75)	1.73 (1.73;1.74)	1.71 (1.70;1.71)	1.68 (1.67;1.69)	1.67 (1.66;1.67)	1.66 (1.64;1.68)	1.68 (1.66;1.70)	<0.0001
Month								
January	33,161	34,110	31,317	34,170	23,370	1,984	1,967	−4.9 (−5.6;−4.2)
	1.72 (1.70;1.73)	1.70 (1.69;1.71)	1.67 (1.66;1.68)	1.65 (1.64;1.66)	1.64 (1.62;1.65)	1.71 (1.67;1.74)	1.64 (1.61;1.68)	<0.0001
February	28,644	30,217	28,164	28,139	19,023	1,868	1,815	−5.4 (−6.2;−4.6)
	1.71 (1.69;1.72)	1.70 (1.69;1.71)	1.67 (1.66;1.68)	1.64 (1.63;1.65)	1.62 (1.60;1.63)	1.62 (1.58;1.65)	1.60 (1.58;1.65)	<0.0001
March	35,744	36,003	30,570	31,583	21,728	2,127	2,142	−5.6 (−6.3;−4.9)
	1.67 (1.65;1.68)	1.66 (1.65;1.67)	1.63 (1.62;1.64)	1.60 (1.59;1.61)	1.57 (1.56;1.59)	1.60 (1.57;1.63)	1.63 (1.60;1.67)	<0.0001
April	26,969	35,394	31,941	28,801	17,433	1,984	2,014	−3.7 (−4.5;−2.9)
	1.64 (1.62;1.65)	1.64 (1.63;1.66)	1.62 (1.61;1.63)	1.59 (1.58;1.60)	1.58 (1.56;1.59)	1.61 (1.58;1.64)	1.59 (1.56;1.62)	<0.0001
May	31,622	36,571	32,901	29,423	20,168	2,146	2,240	−4.6 (−5.3;−3.8)
	1.63 (1.61;1.64)	1.62 (1.61;1.63)	1.60 (1.59;1.61)	1.58 (1.57;1.59)	1.55 (1.54;1.57)	1.57 (1.54;1.61)	1.57 (1.54;1.60)	<0.0001
June	33,357	36,135	31,932	31,061	20,861	2,152	2,144	−5.5 (−6.3;−4.8)
	1.67 (1.66;1.69)	1.67 (1.66;1.68)	1.63 (1.62;1.64)	1.61 (1.60;1.62)	1.58 (1.57;1.59)	1.61 (1.58;1.64)	1.60 (1.56;1.63)	<0.0001
July	19,925	22,097	21,042	21,254	14,334	1,913	1,974	−3.7 (−4.7;−2.7)
	1.67 (1.65;1.69)	1.67 (1.66;1.69)	1.64 (1.62;1.65)	1.62 (1.61;1.64)	1.61 (1.59;1.63)	1.59 (1.55;1.63)	1.63 (1.60;1.67)	<0.0001
August	33,831	33,240	29,855	31,212	21,689	2,225	2,174	−5.1 (−5.8;−4.3)
	1.70 (1.68;1.71)	1.69 (1.68;1.70)	1.67 (1.66;1.68)	1.63 (1.62;1.65)	1.61 (1.60;1.62)	1.64 (1.61;1.67)	1.60 (1.56;1.63)	<0.0001
September	35,672	38,063	33,672	34,074	22,243	2,187	2,236	−5.0 (−5.7;−4.3)
	1.69 (1.68;1.71)	1.69 (1.68;1.70)	1.66 (1.65;1.67)	1.63 (1.62;1.65)	1.61 (1.60;1.62)	1.61 (1.58;1.64)	1.60 (1.57;1.63)	<0.0001
October	34,407	34,852	32,741	35,663	24,424	2,387	2,268	−4.9 (−5.6;−4.2)
	1.69 (1.67;1.70)	1.68 (1.67;1.69)	1.65 (1.64;1.66)	1.63 (1.62;1.64)	1.61 (1.59;1.62)	1.62 (1.59;1.65)	1.60 (1.57;1.63)	<0.0001
November	39,523	39,466	34,968	35,990	26,193	2,465	2,513	−5.3 (−5.9;−4.6)
	1.70 (1.68;1.71)	1.68 (1.67;1.69)	1.66 (1.65;1.67)	1.63 (1.62;1.64)	1.61 (1.59;1.62)	1.60 (1.57;1.63)	1.60 (1.57;1.63)	<0.0001
December	30,668	31,825	27,407	27,613	18,530	2,488	2,463	−4.9 (−5.7;−4.1)
	1.73 (1.71;1.74)	1.72 (1.71;1.73)	1.68 (1.67;1.69)	1.66 (1.65;1.67)	1.64 (1.63;1.66)	1.65 (1.62;1.68)	1.64 (1.61;1.68)	<0.0001

Data are presented as mean and 95% CI per day using a linear mixed model adjusted for gender, age-group (5 year intervals), fasting-status (fasting, nonfasting), hospitals, setting (out-patient, in-patient, in-between-patient), year, month, time of the day (hour) as fixed effects, except the adjustment against the very same predictor (e.g., the analysis between the year and the TG concentration is not adjusted for year) and subject as random effect. The mean and 95% CI are expressed as mmol/l. TG: 1 mmol/l is equivalent to 88.57 mg/dl. *P* for Diff. between Monday and Friday was obtained using pairwise comparisons. Diff., difference between Monday and Friday (negative percentage indicates a higher value on Monday compared with Friday); n, number of observations.

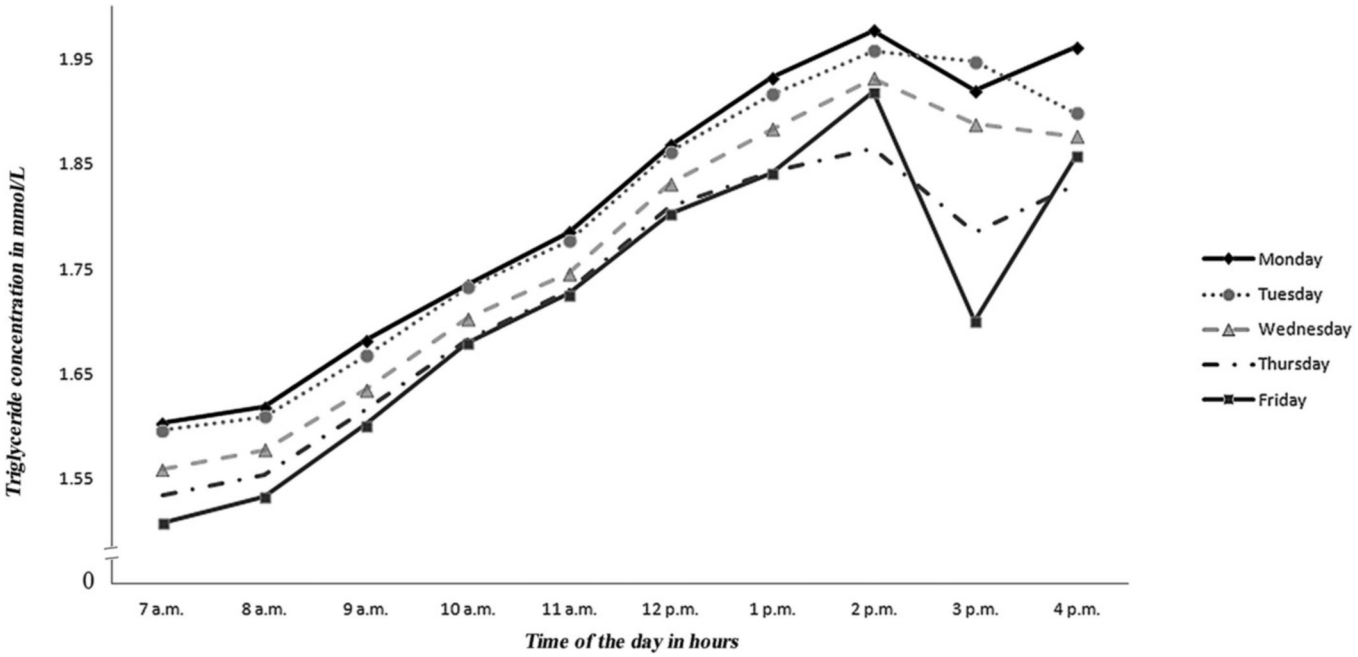

Fig. 2. TG concentration (millimoles per liter) in out-patients from Monday to Friday during laboratory hours (n = 1,251,825). Data are presented as mean using a linear mixed model with gender, age-group (5 year intervals), fasting-status (fasting, nonfasting), hospitals, year, and month as fixed effects and subject as random effect. Numbers of observations range from 57 on Friday at 4:00 PM to 84,510 on Tuesday at 7:00 AM. TG: 1 mmol/l is equivalent to 88.57 mg/dl.

therefore be reasonably generalizable to the entire population in Denmark due to the rather homogenous lifestyle during weekends and non-weekend days among the 5.5 million Danes. Potential deviations from this weekday pattern in other countries around the world may be helpful for identification of its causes.

A limitation of the study is that the study relied solely on samples collected from patients. Certain subgroups, such as the children below 1 year of age cannot be generalized to the general populations, as these children most likely suffer from severe illness. Another limiting factor is the scarcity of patient characteristics, lacking information about the reason for TG measurement, educational concentration, ethnicity, alcohol consumption, dietary intake, and PA; residual confounding may persist. Moreover, based on the observational nature of the data and the lack of recorded exposures in the present study, no causal relationship can be established. Rather, this comprehensive analytic exploration of a large amount of data and the ensuing discussion of key findings are intended to serve as a starting point to generate hypotheses for future research on this topic. An important and initial question is to what extent the variation in TG during weekdays occurs also in other countries or if it is caused by a specific lifestyle in Denmark during the weekends. However, as TG is a component of the metabolic syndrome and a prevalent outcome measurement used in various areas of research, careful planning of future studies may help to avoid undesirable differences attributed to the day and the time of the day the measurement was obtained.

In conclusion, TG concentrations were higher after the weekend and gradually improved during the weekdays. This variation was consistent across all strata, persisted after multiple adjustments, and was likely not attributed to hemodilution or alcohol consumption. We suggest that, in addition to increased concentration of TG that lasts for a few hours after food intake during the day, alterations in food intake and amounts of PA during the weekend increase TG concentrations to a smaller extent, which tracks into the week. A potential difference in research results due to weekday variation may carry implications for public health and may have major implications for future research practice.

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