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RESEARCH ARTICLE

Effects of mammalian *in utero* heat stress on adolescent body temperature

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Abstract

In utero hyperthermia can cause a variety of developmental issues, but how it alters mammalian body temperature during adolescence is not well-understood. Study objectives were to determine the extent to which *in utero* hyperthermia affects future phenotypic responses to a heat load. Pregnant first parity pigs were exposed to thermal neutral (TN) or heat stress (HS) conditions during the entire gestation. Of the resultant offspring, 12 were housed in TN conditions, and 12 were maintained in HS conditions for 15 days. Adolescent pigs in HS conditions had increased rectal temperature and respiration rate (RR) compared to TN pigs, regardless of gestational treatment. Within the HS environment, no gestational difference in RR was detected; however, GHS pigs had increased rectal temperature compared to GTN pigs. As rectal temperature increased, GTN pigs had a more rapid increase in RR compared to the GHS pigs. Adolescent HS decreased nutrient intake, and body weight gain, but neither variable was statistically influenced by gestational treatments. In summary, *in utero* HS compromises the future thermoregulatory response to a thermal insult.

Keywords

Body temperature, epigenetics, heat stress, mammals

History

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Introduction

Environmentally induced hyperthermia or heat stress (HS), results from the imbalance between thermal energy flowing into and out of an animal [1], and negatively impacts health and development in all mammalian species studied. Typical HS responses include slower growth rates, altered metabolism, mortality and altered body composition characterised primarily by increased adipose tissue and reduced skeletal muscle mass [2–4]. Moreover, swine genetic selection for lean tissue accretion rates further compromises HS tolerance as synthesising and maintaining enhanced muscle mass generates increased metabolic heat [5,6]. Consequently, HS is likely one of the primary factors limiting animal protein production and if the frequency of severe hot weather increases as predicted [7] food security will continue to be compromised during the warm summer months, especially in developing countries [4].

In utero hyperthermia negatively impacts a variety of fetal development parameters and can be teratogenic [8]. Furthermore, maternal hyperthermia can have a lasting imprint on offspring growth, behaviour [9], and metabolism [10]. Heat stress during embryonic development either

increases survivability to a future heat load in *Drosophila buzzatii* [11] or improves the future ability to remain euthermic during a thermal insult in birds [12,13]. Further, thermal conditioning immediately following birth can imprint long-term thermotolerance in rodents [14]. In the aforementioned reports, thermotolerance is defined as the ability to maintain a lower or safe body temperature in response to a future heat load. However, the extent to which *in utero* HS affects future body temperature indices in mammals lacks thorough exploration. Study objectives were to characterise HS-induced body temperature indices in adolescent pigs exposed to differing *in utero* thermal environments. We hypothesised that mammalian gestational HS would imprint future thermotolerance to a heat load.

Materials and methods

Animal use in this study was approved by the University of Missouri, Columbia, Animal Care and Use Committee and the Iowa State University Institutional Animal Care and Use Committee.

Gestational environments

Fifteen first parity cross-bred females (Large White × Landrace) were exposed to thermal neutral (TN) (cyclical 15 °C nighttime and 22 °C daytime, 55% relative humidity (RH), $n = 8$), or HS (cyclical 27 °C night-time and 37 °C daytime, 67.5% RH, $n = 7$) conditions in the Brody

environmental chambers at the University of Missouri, Columbia as previously described by Lucy and colleagues [15]. The environmental treatments began six days after insemination and continued until birth (114 days gestation) and resulted in a sustained increase (0.30 °C) in body temperature in pregnant first parity pigs [15]. After parturition, all piglets were exposed to the same environmental conditions (26 to 32 °C) as recommended for neonatal pigs [16]. At weaning, offspring from both TN- and HS-exposed pregnant first parity pigs were transported in an environmentally controlled trailer to Iowa State University for postnatal experiments.

Adolescent environments

Between weaning and 15 weeks of age all animals were commingled and fed *ad libitum* in thermal neutral conditions (based upon body weight) [16]. At 15 weeks of age, adolescent pigs from gestational TN (GTN) ($n = 12$, 67.9 ± 5.3 kg body weight (BW)), and gestational HS (GHS) ($n = 12$, 64.9 ± 3.7 kg BW) exposed pregnant first parity pigs were housed in individual pens (0.61×2.43 m, no wallowing access) in one of two environmentally controlled rooms (TN and HS). Castrated males were selected to reduce the body temperature variability associated with gonadal steroids. In each room, relative humidity (%RH) and ambient temperature (T_a) were recorded every 30 min using two mounted data loggers (EI-WIN-USB, Lascar Electronics, Salisbury, UK) for the length of the experiment. Data loggers were positioned in opposite ends of the rooms to confirm that temperature was uniform throughout each room.

Twelve adolescent males ($n = 6$ GTN, $n = 6$ GHS) were housed in constant TN conditions, and 12 adolescent males ($n = 6$ GTN, $n = 6$ GHS) were maintained in constant HS conditions for 15 days. The TN room was maintained at 22.7 ± 2.5 °C and $71.1 \pm 10.0\%$ RH, while the HS room was maintained at a constant 34.7 ± 2.3 °C and $50.4 \pm 9.7\%$ RH. All pigs were fed a standard commercial diet *ad libitum* consisting primarily of corn and soybean meal formulated to meet or exceed nutritional requirements [17]. Nutrient intake was determined on days 7 and 15, while BW was determined on days -1, 7, and 15. Body weights were used to calculate average daily gain (ADG). Unrestrained respiration rate (RR), skin temperature, and rectal temperature (T_{re}), were measured four times daily (08:00, 12:00, 16:00, 20:00 h) on all animals. Respiration rate in breaths per min (bpm) was determined by counting flank movement over a 1-min interval. Skin temperature (T_{skin}) was determined by calculating the mean temperature of four sites measured at the ear (T_{ear}), shoulder ($T_{shoulder}$), rump (T_{rump}) and tail (T_{tail}) using a calibrated infrared thermometer (Model 42505, Extech Instruments, Waltham, MA). Rectal temperature was determined with a calibrated and lubricated thermistor thermometer (Welch Allyn SureTemp® Plus, Skaneateles Falls, NY) inserted approximately 10 cm into the rectum of unrestrained pigs. Due to the constant heat load, and lack of statistical hourly differences the hourly body temperature indices (RR, T_{skin} , T_{re}) were condensed into daily averages. A thermal circulation index (TCI) was calculated using T_{re} , temperature at one of the skin sites or T_{skin} , and T_a , and was used as an indicator of blood

and heat transfer to a particular area of the skin under steady state thermal conditions described for agricultural species [18]:

$$TCI = (T_{skin} - T_a) / (T_{re} - T_{skin}).$$

Statistics

All data were analysed using the PROC MIXED procedure in SAS 9.3 (SAS Institute, Cary, NC). Statistical model components included gestational environment (GTN, GHS), adolescent environment (TN, HS), day (1–15), and all possible interactions. All interactions, regardless of significance level, were included in the model and pregnant first parity pig was used as a random effect. Initial body weight was used as a covariate for analysis of final body weight and body weight gain. For repeated analyses, each pig's respective parameter was analysed using repeated measures with an auto-regressive covariance structure with day as the repeated effect.

Linear ($y = mx + b$) and quadratic models were created using JMP (SAS Institute) to determine the relationship between RR (y - axis) and T_{re} (x - axis). Slope and correlation coefficient values from each model were similar, so the linear regression was used for analysis. Slope was obtained for individual animals using all collected data points and analysed using the mixed procedure in SAS 9.3, with slope as the dependent variable, and gestational environment (GTN, GHS), adolescent environment (TN, HS) and the interaction of gestational environment and adolescent environment as fixed effects. Pregnant first parity pig was used as a random effect. All interactions, regardless of significance level were kept in the model. Data are presented as least squares means and statistical significance was defined as $p \leq 0.05$, and a tendency was defined as $0.05 < p \leq 0.10$.

Results

Thermal indices

There were no gestational differences detected in overall RR ($p > 0.14$), but there was a large RR increase (~ 2 fold, $p < 0.01$) for adolescent pigs in HS conditions compared to TN controls (Table I, Figure 1A). Regardless of gestational treatment, adolescent pigs in HS conditions had increased T_{re} ($p < 0.01$, 0.33 °C, Table I) compared to TN-housed pigs (Figure 1B). An overall gestational by adolescent interaction ($p < 0.01$) indicated that GHS pigs had a larger increase in T_{re} during adolescent HS compared to GTN pigs (0.50 versus 0.16 °C, Table I, Figure 1C). A gestational environment by adolescent environment by day interaction was not observed for T_{re} (Figure 1B).

No overall differences were detected at any specific skin temperature site or T_{skin} when comparing gestational treatments; however, all were increased for adolescent pigs housed in HS conditions compared to TN conditions by 17 to 19% (Table I, Figure 2). There were also no gestational by adolescent interactions detected for T_{ear} , $T_{shoulder}$, T_{rump} , T_{tail} or T_{skin} . Thermal circulation index was similar in adolescent pigs from differing environments when measured at the ear and tail. However, TCI was increased 50 to 52% at the rump and T_{skin} in heat-stressed pigs compared to pigs in TN conditions. Overall, pigs from GHS had increased TCI_{tail}

Table I. Effects of gestational and adolescent thermal environments on body temperature indices in growing pigs.

Parameter	Environments				SD	<i>p</i>		
	GTN-TN ¹	GHS-TN ²	GTN-HS ³	GHS-HS ⁴		G ⁵	A ⁶	G × A
RR ⁷ (bpm)	52	45	93	90	23	0.14	<0.01	0.52
T _{re} ^{8,9} (°C)	39.35 ^a	39.27 ^a	39.51 ^b	39.77 ^c	0.31	0.15	<0.01	<0.01
T _{ear} (°C)	30.87	30.64	36.51	36.77	2.23	0.96	<0.01	0.39
T _{shoulder} (°C)	31.60	31.43	36.82	37.12	1.90	0.79	<0.01	0.26
T _{rump} (°C)	31.36	31.30	37.33	37.50	1.85	0.86	<0.01	0.61
T _{tail} (°C)	31.42	31.31	36.99	37.27	1.85	0.66	<0.01	0.30
T _{skin} ¹⁰ (°C)	31.32	31.17	36.91	37.19	1.75	0.78	<0.01	0.33
TCI _{ear} ¹¹	1.09	1.02	1.24	0.92	1.48	0.14	0.84	0.30
TCI _{shoulder}	1.21	1.16	1.71	1.42	3.07	0.29	0.06	0.32
TCI _{rump}	1.19	1.10	1.58	1.90	3.66	0.46	<0.01	0.11
TCI _{tail}	1.15 ^a	1.14 ^a	0.84 ^a	2.10 ^b	2.74	0.03	0.25	0.02
TCI _{skin}	1.12	1.07	1.51	1.78	2.07	0.38	<0.01	0.20

¹Gestational thermal neutral pigs in adolescent thermal neutral conditions

²Gestational heat stress pigs in adolescent thermal neutral conditions

³Gestational thermal neutral pigs in adolescent heat stress conditions

⁴Gestational heat stress pigs in adolescent heat stress conditions

⁵Gestational environment

⁶Adolescent environment

⁷Respiration rate

⁸Temperature

⁹Rectal

¹⁰Average skin temperature

¹¹Thermal circulation index

a,b,c *p* < 0.05

(*p* = 0.03, 16%) compared to GTN pigs, but this was primarily due to the gestational by adolescent interaction (*p* = 0.02) indicating that the GHS pigs had a larger increase (150%) during HS compared to GTN pigs (Table I). Adolescent HS tended (*p* < 0.06) to increase TCI_{shoulder} (32%, Table I). There was no gestational effect or gestational by adolescent environment interaction detected for TCI_{shoulder}, TCI_{rump}, TCI_{ear}, or TCI_{skin}.

Regression analysis

With regard to the relationship between T_{re} and RR, GTN pigs had a steeper slope (12 bpm/1 °C) compared to GHS pigs (*p* < 0.01, Figure 3). No gestational environment by adolescent environment interaction differences were detected for this relationship (*p* = 0.15).

Growth parameters

Overall nutrient intake did not differ between gestational treatments (2.52 kg/day), but it was reduced by 25% (*p* < 0.01) in the adolescent HS conditions compared to the TN controls (Table II). Animal growth was not affected by gestational thermal treatments (0.70 kg/day), but decreased 34% (*p* = 0.04) in HS pigs compared to those in TN conditions (Table II). There were no gestational or adolescent treatment effects (*p* > 0.16) detected for feed efficiency (0.27 kg gain/kg feed, Table II).

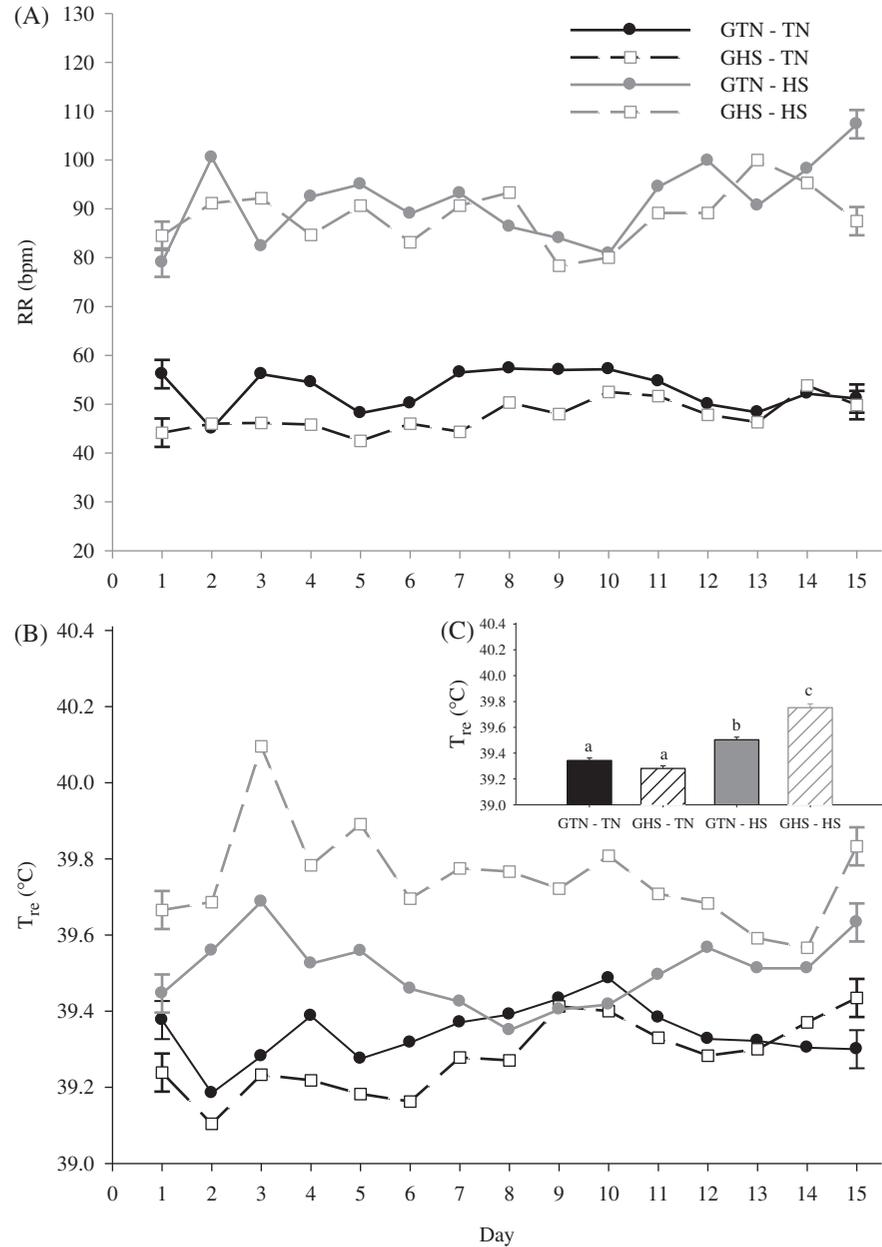
Discussion

Although HS is a serious economic burden and negatively impacts human health and animal welfare, it is also a primary constraint to efficient livestock growth and development. While this is the case in most geographical areas of North America, it is particularly true in tropical and subtropical regions of the world where many developing

countries are located [19,20]. As a result, these regions experience extended periods of HS compared to temperate climates (i.e. pigs could be exposed to HS during both gestation and the growing phase), making HS not only an economic issue, but also a serious food security and humanitarian concern [19]. Despite the fact that HS constitutes a well-documented physiological insult with global implications, understanding the epigenetic impact of HS during gestation on future progeny is not well-defined in mammalian species.

A variety of prenatal insults can have permanent effects on postnatal phenotypes and has been evaluated with regard to metabolic dysfunction [10] and teratogenicity [8]. Experimental models such as intrauterine growth retardation indicate that future growth parameters [21,22], body composition [23], and post-absorptive metabolism can be markedly altered by *in utero* insults [10]. Hales and Barker [24] first introduced the idea of a 'thrifty phenotype', whereby fetal malnutrition causes maladaptive programming which results in glucose-sparing metabolism that persists in the offspring. Similar effects can be observed during thermal stress where exposure of unicellular organisms [25], insects [11] and birds [12,13,26,27] to elevated temperatures in previous generations or *in ovo* alters postnatal survivability and/or body temperature indices. This 'thermal conditioning' has also been demonstrated in rodents exposed to HS conditions shortly after birth [14]. This is particularly true for imprinting thermotolerance; defined as the enhanced ability to maintain a lower or safer body temperature in response to a future heat load. However, the degree to which *in utero* HS affects thermotolerance in mammals during adolescence is not well understood. Herein, we demonstrate that *in utero* HS impairs the future HS response in a mammalian model, which was contrary to our hypothesis that thermotolerance would have been imprinted.

Figure 1. Effects of gestational and adolescent thermal environments on the temporal changes in (A) respiration rate (RR), (B) rectal temperature (T_{re}), and (C) T_{re} averaged by gestational and adolescent environment in growing pigs. Gestational heat stress (GHS), gestational thermal neutral (GTN), adolescent thermal neutral conditions (TN), adolescent heat stress conditions (HS). Error bars on day 1 and day 15 of the line indicate ± 1 SEM. Different letters (a,b,c) above vertical bars in 1C indicate significant differences ($p < 0.05$).



No overall gestational differences were detected in any body temperature variable during adolescent TN conditions. However, during adolescent HS, pigs derived from heat-stressed first parity pigs had an increase in a variety of body temperature indices, most notably, core temperature (T_{re}). That gestational differences were only detected in HS conditions is not surprising, as epigenetic alterations impacting body temperature likely need a thermal insult to be expressed. This sort of HS-induced phenotype is similar to what has been reported in poultry [13]. In stark contrast to the aforementioned literature that suggests thermal 'imprinting' increases future temperature tolerance, gestationally heat-stressed pigs actually became more hyperthermic during a future HS compared to GTN pigs (Figure 1B). Reasons for the species difference are not clear but of obvious biological and practical interest. Further, given the physiological and phylogenetic similarities between humans and pigs, these data could predict the human response to *in utero* HS.

The gestation difference in T_{re} during adolescent HS averaged 0.26°C and suggests that pigs originating from chronically heat-stressed pregnant first parity pigs are less able to adapt to a future HS compared to pigs derived from TN dams (Figure 1B). The increase in T_{re} observed in GHS pigs during adolescent HS is corroborated by numerical, but not statistically significant differences in T_{skin} (Figure 2). The primary numerical gestational treatment differences in T_{skin} occurred between days four and nine of the experiment, which temporally coincides with the largest difference in T_{re} (Figure 1B). As expected, constant adolescent HS markedly increased RR as pigs (in the absence of opportunity for behavioural wetting) utilise panting as their primary route of latent heat loss [3,28]. Despite GHS pigs having increased T_{re} during HS conditions, RR was similar between gestational treatments within the adolescent HS group. Regardless of the lack of gestation RR differences, the overall relationship (specifically the slope relationship) between T_{re} and RR was steeper (33%) for GTN compared to GHS pigs. In other

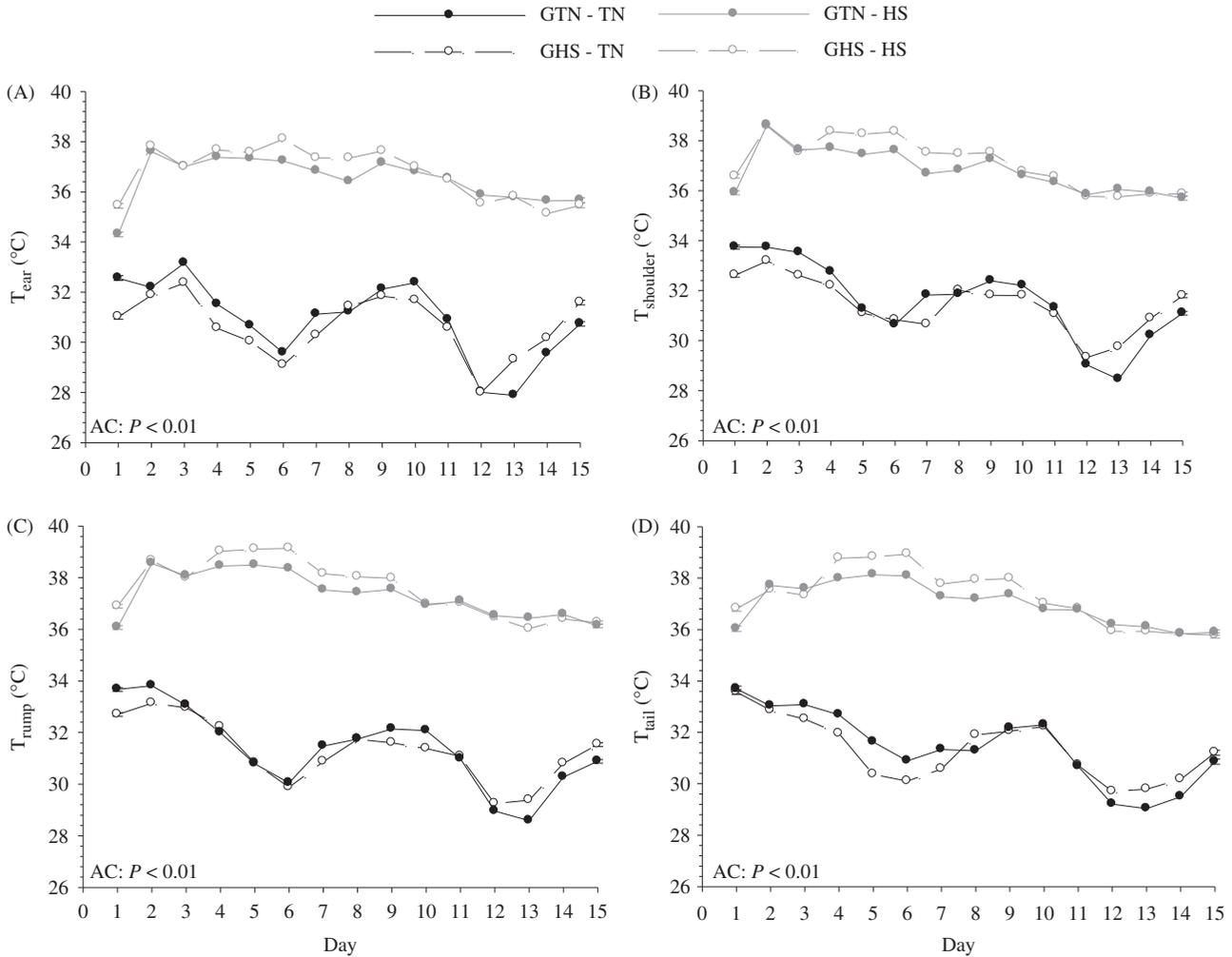


Figure 2. Effects of gestational and adolescent thermal environments on the temporal changes in (A) ear skin temperature (T_{ear}), (B) shoulder skin temperature ($T_{shoulder}$), (C) rump skin temperature (T_{rump}), and (D) tail skin temperature (T_{tail}) in growing pigs. Gestational heat stress (GHS), gestational thermal neutral (GTN), adolescent thermal neutral conditions (TN), adolescent heat stress conditions (HS), adolescent conditions (AC). Error bars on day 1 and day 15 of the line indicate ± 1 SEM. p Values in each figure represent T_{skin} differences comparing adolescent TN and HS exposed animals regardless of gestational treatment.

Figure 3. Linear regression ($y = mx + b$) of respiration rate (RR) as a function of rectal temperature (T_{re}) for gestational thermal neutral (GTN) and gestational heat stress (GHS) exposed pigs, regardless of adolescent environment. Coefficient of determination (R^2), and slope (m) is presented for each regression line.

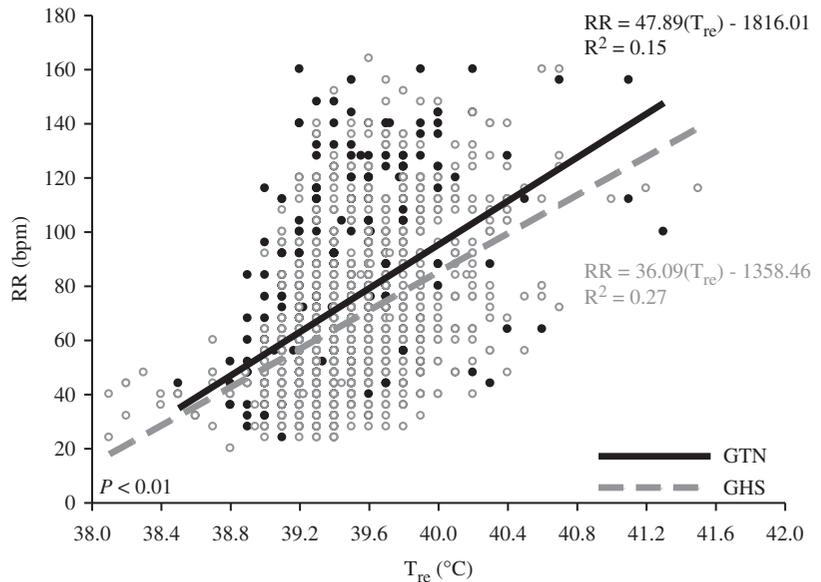


Table II. Effects of gestational and adolescent thermal environments on production parameters in growing pigs.

Parameter	Environments				SD	<i>p</i>		
	GTN-TN ¹	GHS-TN ²	GTN-HS ³	GHS-HS ⁴		G ⁵	A ⁶	G × A
Initial BW (kg)	68.5	66.3	67.3	63.5	4.6	0.17	0.31	0.68
Final BW (kg)	80.1	77.5	76.4	72.5	6.3	0.16	0.04	0.70
NI (kg/d) ⁸	2.87	2.89	2.24	2.07	0.56	0.71	<0.01	0.61
BW gain (kg/d) ⁷	0.92	0.75	0.68	0.42	0.29	0.16	0.04	0.70
Gain:Feed (kg/kg) ⁹	0.34	0.25	0.32	0.15	0.12	0.10	0.16	0.34

¹Gestational thermal neutral pigs in adolescent thermal neutral conditions

²Gestational heat stress pigs in adolescent thermal neutral conditions

³Gestational thermal neutral pigs in adolescent heat stress conditions

⁴Gestational heat stress pigs in adolescent heat stress conditions

⁵Gestational environment

⁶Adolescent environment

⁷Body weight gain

⁸Nutrient intake

⁹Feed efficiency

words, the RR response to increasing T_{re} occurred more rapidly in the GTN pigs than for GHS pigs (Figure 3). The overall blunted respiratory response in GHS animals may have compromised the effectiveness of heat dissipation and resulted in a higher T_{re} . This may also be due to epigenetic modification(s) that produce an increase in their body temperature ‘set-point’ where the GHS pigs experience a rise in T_{re} without a subsequent increase in RR or other heat dissipating mechanisms to mitigate the effect. An alternative explanation may be that GHS animals are more tolerant to a higher body temperature and do not need to initiate respiratory cooling mechanisms as quickly as controls.

Consistent with previous reports [3,5,29,30], adolescent HS in this study caused a reduction in a variety of growth variables compared to TN conditions. Specifically, HS reduced final BW (6%), nutrient intake (25%), and BW gain (34%); however, gestational treatment did not statistically impact these variables. Feed efficiency was not influenced by gestational conditions, and surprisingly not affected by adolescent HS. However, this measure is based upon gross body weight change and does not take into account body composition differences, which are important since HS reorganises nutrient partitioning priorities and the hierarchy of tissue synthesis [4].

The T_{re} increase in the GHS pigs may imply that gestational hyperthermia results in increased susceptibility to future heat loads. Further, the relationship between T_{re} and RR (Figure 3) suggests that GHS were less effective at utilising enhanced respiration as a means to dissipate excess heat. Consequently, based upon typical measures of thermoregulation, it could be argued that gestational HS compromises tolerance to a future heat load. Yet, despite the increased T_{re} in response to adolescent HS, pigs derived from *in utero* HS had similar nutrient intake compared to GTN pigs, suggesting that GHS pigs may have tolerated higher body temperatures better than controls (potentially programmed prenatally). Although no nutrient intake differences were observed for GHS and GTN pigs, ADG was numerically but not statistically reduced ($p > 0.15$) in GHS compared to GTN pigs by 215 g/day, regardless of adolescent environment. This reduction combined with a possible increase in core temperature set-point has many bioenergetic implications, which

if maintained throughout life could result in significant economic losses for the swine industry. If GHS animals are prenatally programmed to maintain an increased core temperature set-point during a future heat load, this would theoretically increase maintenance costs which would have implications for nutrient partitioning, feed efficiency, feed intake, and barn throughput.

Although it is tempting to speculate that GHS animals have an increase in maintenance costs due to greater body temperature (at least during HS), we only measured growth variables to provide a context for the body temperature measurements. Accordingly, the growth data need to be interpreted with care, as determining the effects of gestational HS on future production was not a primary objective and would certainly require more measurements and animals per treatments to make meaningful conclusions. Additionally, whether or not these temperature differences are maintained (or augmented) during a diurnal heat pattern compared to a constant heat load would be of significant interest. Clearly this experiment needs to be repeated with more of an emphasis placed on continuous body temperature indices obtained in both TN and HS conditions. Regardless, the results suggest that the well-documented decrease in nutrient intake and increase in RR associated with increased core body temperature [2,3,5,28,29,31] may be partially influenced by fetal programming. Furthermore, the phenotypic responses to HS are variable [31,32], and it is tempting to hypothesise that a portion of this variation may be due to epigenetic imprinting [28].

Conclusion

Maternal hyperthermia can have lasting effects on developmental patterns. Further, it can alter future growth and behaviour, and we have now demonstrated that it alters the body temperature response to a heat load. Specifically, animals that experienced *in utero* HS became more hyperthermic in response to a future heat load. This has obvious bioenergetic implications in both human health and animal agriculture. A prerequisite to developing HS mitigation strategies is a better understanding of how HS epigenetically alters physiological responses throughout all stages of the life

cycle. Further, how this compromised thermoregulatory response during HS influences metabolic function, future development, and bioenergetics is unknown and will be the focus of upcoming investigations.

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Declaration of interest

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