Published in final edited form as:

Behav Neurosci. 2009 June ; 123(3): 607–613. doi:10.1037/a0015064.

Effects of the First Prepulse on the Blink Response to a Startling Noise

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Abstract

Startle is inhibited when a startling stimulus follows 30–300 ms after a weak prepulse. Prepulse inhibition (PPI) is an operational measure of sensorimotor gating and is deficient in several neuropsychiatric disorders. Previous reports argue both for and against a learned component to the inhibitory effects of prepulses, but this issue has yet to be fully investigated using stimuli that most commonly detect PPI deficits in clinical populations. If the inhibitory impact of a prepulse is learned, PPI should not be evident when the prepulse is the first stimulus experienced by the subject. Eyeblick electromyography in normal adults was recorded after either a 118 dB(A) 40-ms noise pulse alone (PA) or the same pulse preceded 120 ms by an 86 dB(A) 5-ms noise prepulse (pp + P). In 25 subjects (Order 1), Trial 1 was a PA, and Trial 2 was a pp + P; 23 subjects experienced the opposite order (Order 2). In 34 subjects, Trials 1 and 2 were both PA (control order). Background was 70 dB(A). Startle magnitude increased from Trial 1 to 2 if no prepulse was presented (control order). Compared with the control order, startle inhibition by prepulses was evident in both Orders 1 and 2, and was more robust in Order 2 (first trial = pp + P). Startle magnitude was significantly lower on pp + P than on PA trials in Order 2 but not Order 1 ($F < 1$). Prepulses inhibit startle on the first pairing with a startling pulse, an effect that cannot be explained by learning.

Keywords

acoustic startle; learning; prepulse inhibition; reflex latency; sensorimotor gating

Inhibition of the acoustic startle reflex by discrete prepulses (*prepulse inhibition*; PPI) is deficient in several neuropsychiatric disorders (Braff et al., 1978; Braff, Swerdlow, & Geyer, 1999; Hoenig et al., 2005; Sobin, Kiley-Brabeck, & Karayiorgou, 2005; Kumari, Soni, & Sharma, 1999; Ludewig, Geyer, & Vollenweider, 2003; Swerdlow et al., 1995; Valls-Sole, Munoz, & Valldeoriola, 2004; cf. Braff, Geyer, & Swerdlow, 2001). PPI occurs without any instructional set or attentional task, and does not diminish after repeated prepulse presentations, and thus has been described as a measure of “automatic” inhibition or sensorimotor gating (Graham, 1975; Ison, Hammond, & Krauter, 1973). However, it has been clearly demonstrated that PPI can also be modified by attentional demands or states (cf.

Acocella & Blumenthal, 1990; Anthony & Graham, 1985; Hoffman, 1997; van der Linden, Massar, Schellekens, Ellenbroek, & Verkes, 2006), and this sensitivity to higher cognitive processes together with some reports that PPI can change over time (Crofton, Dean, Sheets, & Peele, 1990; Gewirtz & Davis, 1995) raise the possibility that at least some of the inhibitory effects of the prepulse on startle magnitude reflect a form of “learning.” Certainly, the interpretation of PPI deficits in patient populations, and of the likely neural basis for such deficits, would be very different if we viewed this inhibitory process as “automatic” versus “learned.”

Some early studies of the rat startle reflex have suggested that the inhibitory effects of prepulses could be detected on the initial pairing of an acoustic prepulse and pulse, provided that the prepulse was relatively intense (e.g., 22 dB over background noise; Ison et al., 1973). Krauter, Leonard, and Ison (1973) further demonstrated that cross-modal PPI could be detected on the first exposure to a loud acoustic prepulse (a response-eliciting tone 40 dB over ambient background) followed 120 ms by a corneal air puff startle stimulus. In both of these reports (Ison et al., 1973; Krauter et al., 1973), the authors suggested that the inhibitory effects of weaker prepulses might be detected only after previous exposure to startling stimuli (but should not require pairings of prepulses and pulses). The findings were viewed as evidence that prepulses inhibit startle by mechanisms that do not require learning, leading Hoffman and Ison (1992) to conclude, “although reflex modification and classical conditioning share some common features ... [they] are quite distinct behavioral phenomena” (p. 85). Confirmatory data from humans were reported by Graham (1975), in the form of acoustic startle blink waveforms from a single subject, whose blink response on Trial 1 (acoustic prepulse + pulse) was substantially smaller than Trial 2 (pulse alone).

Since these early reports, many studies have reported PPI deficits in clinical populations (cf. Braff et al., 2001; Swerdlow, Weber, Qu, Light, & Braff, 2008). The predominant types of stimuli in these reports have been unimodal discrete acoustic prepulses and pulses, using nonstartling prepulses that were 8–16 dB over background. Despite early evidence that at least some components of human PPI are automatic, that is, not learned, we were unable to find a published report that demonstrated this finding using a single prepulse exposure in humans with stimuli typically used to detect PPI deficits in clinical populations. There are reasons to believe that relatively subtle differences in stimulus conditions can determine whether inhibition does or does not require “learning”: For example, in apparent contrast to the reports of Ison et al. (1973) and Krauter et al. (1973), startle inhibition by noise gaps (rather than noise bursts) may require previous experience of the gap–pulse pairing (Crofton et al., 1990).

There are several logistical complexities to studies of “first prepulse” effects. First, startle variability across subjects is greatest on the initial trial. For this reason, responses to the initial startle trial are often omitted from data analyses. However, to fully address the contribution of learning to startle response characteristics, it is important for there to be no previous exposure to the startle or prepulse stimuli; thus, the initial trial response—despite its inherent variability—must be analyzed. Second, many processes other than PPI can contribute to changes in startle magnitude, including reflex sensitization and habituation. When assessing changes across the first two consecutive startle trials (to compare startle

with vs. without a prepulse), it is difficult to attribute changes in startle magnitude to one of these processes, rather than a combination of these processes.

Despite these potential complexities, we attempted to determine whether acoustic PPI in humans occurs on the first exposure to a prepulse that is 16 dB over background. If PPI in humans is learned, then it should not be evident on the first prepulse exposure because at least one pairing of stimuli should be required for learning to occur. We also examined the potential involvement of learning in the reduction in reflex latency by prepulses, termed *latency facilitation*, which might be distinct from an involvement of learning on PPI of startle magnitude (Graham & Murray, 1977).

Method

Eyeblink electromyography (EMG) was recorded in 98 healthy, carefully screened, right-handed adults (see Table 1). Phone screening excluded subjects endorsing a history of substance abuse or other mental illness, schizophrenia in a first-degree relative, other significant medical illness (e.g., cancer, diabetes, heart disease, HIV), current medications, history of seizure, open head injury or closed head injury with loss of consciousness >1 min, or hearing or visual impairment. Appropriate subjects completed a screening visit, where phone questions were repeated, together with detailed demographic, medical, neurologic, and psychiatric screening (Structured Clinical Interview for *DSM-IV*—Nonpatient Edition; First, Spitzer, Gibbon, & Williams, 1997); subjects completed urine toxicology and hearing tests (exclusion: impairment at 40 dB(A), 1 kHz). Informed consent was obtained. Subjects also completed various personality questionnaires.

Subjects sat in a comfortable chair and received no instructions related to any attentional or cognitive task. Two miniature Ag/AgCl electrodes were positioned below and to the outer canthus of each eye over orbicularis oculi; ground electrode was positioned behind the left ear on the mastoid ($R < 10$ kW). Eyeblink was measured using EMG recordings. EMG activity was rectified, band-pass filtered (100–1000 Hz) and 60 Hz notch filtered, digitized, and 250 1-ms readings were recorded starting at startle stimulus onset. A background 70 dB(A) white noise was continuous throughout the session. Trials consisted of a 118 dB(A) 40-ms noise pulse alone (PA), or the same PA preceded 120 ms by an 86 dB(A) 5-ms noise prepulse (pp + P). The intertrial interval was 15 s. In 25 subjects (Order 1), the sequence was Trial 1 = PA, Trial 2 = pp + P; in 23 subjects, trial order was reversed (Order 2). To assess the normal patterns of reflex habituation or sensitization during Trials 1 and 2, in 34 subjects, both trials were PA (control order; see Figure 1). These trials were part of a routine screening session for subsequent pharmacological challenge studies. All female subjects were tested on the first day of their menstrual cycle, when we have previously detected no significant sex differences in PPI (Swerdlow, Hartman, & Auerbach, 1997).

Analyses first examined changes in startle magnitude and latency across Trials 1 and 2, when both stimuli were simple startle pulses (control order). Analyses then compared startle magnitude, PPI, and reflex latency between subjects tested in Order 1 versus Order 2. Where possible, comparison subgroups were matched for comparable values (magnitude or latency) on PA trials to increase the sensitivity of detecting the effects of prepulses.

PPI was defined as $(100 - [100 \times \text{magnitude on prepulse trial} / \text{magnitude on pulse alone trials}])$. Peak and onset startle latency were also measured for PA and pp + P trials. No significant main or relevant interaction effects were detected with eye side (right vs. left) or gender; thus, data were collapsed across sides and gender and analyzed by mixed design analyses of variance (ANOVAs) using trial type as within-subject factors. Alpha was .05.

Results

Analyses first assessed changes in startle magnitude and latency in the control order, in which Trials 1 and 2 were both PA (see Figure 2). ANOVA of startle magnitude revealed a significant effect of trial number (magnitude on Trial 2 > Trial 1), $F(1, 33) = 4.59, p < .04$. ANOVA of peak startle latency also revealed a significant effect of trial number (latency on Trial 1 > Trial 2), $F(1, 33) = 21.55, p < .0001$; the same effect was evident with startle onset latency ($p < .0001$). Thus, in the control sequence of two consecutive PA trials, startle magnitude increased and latency decreased.

Analyses next compared subjects tested in Order 1 versus Order 2. ANOVA of startle magnitude (Figure 3A) revealed a significant effect of trial type (PA vs. pp + P), $F(1, 44) = 15.09, p < .0005$, and no effect of trial order, $F(1, 44) = 2.00, ns$, but a significant interaction of Trial Type $\times$ Order, $F(1, 44) = 8.07, p < .007$. Post hoc comparisons revealed a significant effect of trial number among subjects tested in Order 2 (i.e., pp + P < PA when pp + P is followed by PA), $F(1, 21) = 20.00, p < .0003$, but not among those tested in Order 1 (PA followed by pp + P: $F < 1$). A between-groups comparison revealed no difference in startle magnitude on Trial 1 between subjects whose first trial was a PA versus a pp + P ($F < 1$). Startle magnitude on the first PA trial was significantly greater in Order 2 (i.e., Trial 2) compared with Order 1 (i.e., Trial 1), $F(1, 46) = 4.34, p < .05$.

The apparent PPI advantage of Order 2 versus Order 1 was confirmed by direct analysis of %PPI (see Figure 3C and 3D), which revealed a significant effect of trial order (Order 2 > Order 1), $F(1, 46) = 7.27, p < .01$; this difference in %PPI persisted when order groups were balanced (as shown in Figure 3B) for startle magnitude on the initial PA trial ($p < .015$). The same order effect was evident in an ANOVA of PPI difference scores (startle magnitude on PA minus pp + P trials: $p < .007$).

To assess the possible impact of reflex sensitization (an increase in startle magnitude from Trial 1 to Trial 2, as shown above for the control order) on PPI, we compared subjects tested in Orders 1 and 2 with subjects tested in the control order (see Figure 3E and 3F). Trials in the control order were treated as if one was a pp + P trial, and a %PPI value was calculated. In the comparison of Order 1 versus the control order, Trial 2 was always treated as the pp + P trial, and in the comparison of Order 2 versus control order, Trial 1 was always treated as the pp + P trial (one control subject was excluded for a %PPI value of $-1133.3, > 25 SD$ below the group mean). In both cases, the actual presence of a prepulse resulted in significantly greater PPI; for Order 1 versus control order, ANOVA revealed a significant effect of trial order, $F(1, 56) = 4.76, p < .035$, and the same was true for Order 2 versus control order, $F(1, 54) = 6.56, p < .015$. In other words, whether the prepulse was included in

Trial 1 or Trial 2, the resulting amount of startle inhibition could be detected in comparison to a control trial that lacked a prepulse.

Analyses of startle latency first compared Order 1 versus Order 2. Peak startle latency could not be detected on pp + P trials in four subjects because of startle values of zero. Analysis of the remaining subjects (see Figure 4) revealed a significant effect of trial type ($PA > pp + P$), $F(1, 40) = 10.06$, $p < .003$, no significant effect of trial order ($F < 1$), but a significant interaction of Trial Type $\times$ Order, $F(1, 40) = 8.89$, $p < .005$. Post hoc comparisons revealed significant latency facilitation among subjects tested in Order 1, $F(1, 22) = 15.06$, $p < .0009$, but not among subjects tested in Order 2 ($F < 1$). Peak latency on PA trials was marginally longer in subjects tested in Order 1, $F(1, 46) = 3.91$, $p < .054$. Comparison of Trial 1 values revealed peak latency $M = 75.48$ ms ($SEM = 1.91$) for PA trials (Order 1) versus $M = 69.79$ ms ($SEM = 1.85$) for pp + P trials (Order 2). This difference did not reach statistical significance, $F(1, 43) = 2.49$, *ns*. A similar pattern was detected for onset latency ($M = 43.82$ ms, $SEM = 1.94$) for PA trials (Order 1) versus pp + P trials (Order 2; $M = 39.19$ ms, $SEM = 1.33$), $F(1, 44) = 2.08$, *ns*.

The amount of latency facilitation (latency on PA trials minus pp + P trials) was significantly greater in Order 1 compared with Order 2, $F(1, 42) = 9.26$, $p < .005$; this difference persisted when order groups were balanced for identical PA magnitude ($p < .005$) and for comparable peak startle latency ($p = .01$). Statistical analyses of startle onset latency yielded findings that paralleled each of those for peak startle latency (see Figure 3).

As noted above, when Trials 1 and 2 were both PA (control order), reflex latency declined significantly from Trial 1 to Trial 2. To assess the impact of this effect on the observed differences between Orders 1 and 2, we conducted the same “sham” analysis described above for analyses of PPI: Trials in the control order were treated as if one was a pp + P trial. In the comparison of Order 1 versus the control order, the powerful reduction in latency between Trials 1 and 2 (noted above, in the control order) appeared to obviate the expression of prepulse-induced latency facilitation: ANOVA revealed a significant effect of Trial 1 versus Trial 2, $F(1, 55) = 36.04$, $p < .0001$, that was independent of the presence of a prepulse (Trial Number $\times$ Order interaction), $F(1, 55) = 1.62$, *ns*; the same pattern was evident for onset latency (Trial 1 vs. 2), $F(1, 55) = 53.79$, $p < .0001$, and Number $\times$ Order interaction, $F(1, 55) = 1.32$, *ns*. In the comparison of Order 2 versus control order, the powerful effect of trial number was blocked when Trial 1 included a prepulse: The comparison of Order 2 versus control order revealed significant effects of trial number, $F(1, 51) = 7.15$, $p = .01$, and a significant Number $\times$ Order interaction, $F(1, 51) = 8.94$, $p < .005$. This interaction reflected the fact that mean reflex latency declined from Trials 1 to 2 in the control order from 70.97 ($SEM = 1.78$) to 63.33 ($SEM = 1.08$), but not in Order 2 ($M = 69.79$, $SEM = 1.85$, to $M = 70.11$, $SEM = 1.42$).

Discussion

In the present study, the properties of the startle reflex were compared across two startle trials, one of which contained an isolated startle stimulus, and the other of which contained that same startle stimulus preceded 120 ms by a prepulse. Within subjects, it could be

observed that the prepulse accompanied a reduction of startle magnitude only if the prepulse was present in the first trial, and accompanied a reduction in startle latency only if the prepulse was presented in the second trial.

Independent of prepulses, reflex amplitude increased and latency decreased from Trial 1 to Trial 2. Prepulse effects were thus examined by comparing startle characteristics in subjects who did versus did not experience a prepulse in Trial 1 or 2. These comparisons confirm the presence of PPI when a prepulse was present on the first trial, but also demonstrated that prepulses significantly affected startle magnitude when presented on the second trial, by blocking the expression of startle sensitization. These comparisons also suggest that prepulses reduced startle latency when presented on the first trial, based on the absence of the expected reduction in reflex latency from Trials 1 to 2.

Addressing the main hypothesis tested in this study, PPI was evident when the prepulse was the first stimulus experienced in a test session. It is not parsimonious to attribute any of the startle-inhibiting effects of this prepulse to learning processes because subjects had not previously experienced a pairing of the prepulse and pulse. However, arriving at this conclusion required complex and somewhat convoluted analyses based on the dynamic interplay of multiple startle variables even in the span of two consecutive startle trials. Certainly, many of these changes have been reported previously (e.g., Graham, 1975; Ison & Hammond, 1971; Ison et al., 1973). Startle sensitization was evident in increased startle magnitude from Trial 1 to 2, and was accompanied by a reduction in reflex latency. According to dual process theory (Groves & Thompson, 1970), habituation was also occurring at this time, even if its effects were obscured by sensitization. Latency also declined markedly from Trial 1 to 2; this pattern of increased reflex magnitude and decreased reflex latency is likely to be mechanistically distinct from that typically detected with prepulses, which reduce both reflex magnitude and latency. When prepulses were introduced into Trial 1 or 2, their effects on reflex magnitude and latency were superimposed on the magnitude sensitization and habituation and latency reduction that resulted from the effects of trial order. In truth, we have no way of knowing whether the observed results reflected simple additivity or a more complex interaction of prepulse-dependent and -independent processes.

More generally, the effects of prepulses on startle magnitude must be considered in the context of ongoing processes of sensitization and habituation. Many groups have emphasized the importance of considering levels of startle magnitude on PA trials when comparing PPI across different groups or treatment conditions (cf. Swerdlow et al., 2008). Perhaps less is discussed about the need to consider changes in PPI over time as a function of interactions with sensitization and habituation; conceivably, apparent effects of drugs or other manipulations on PPI across a test session might reflect, in part, the impact of these drugs on reflex sensitization or habituation. Because of this, studies evaluating drug effects on PPI typically use session designs and stimulus parameters that minimize reflex habituation and sensitization, or that permit an analysis of PPI changes over blocks of trials. The present study demonstrates that PPI can occur on the first startle trial, which is the only trial within a session that can be considered to be completely free from the effects of either habituation or sensitization.

Perhaps most remarkable are the many levels of neural and behavioral plasticity elicited in humans by a single acoustic stimulus, as detected by changes in reflex magnitude and latency, and their interactions with a weak prepulse. It is somewhat astonishing that, in this dynamic environment, it is possible to identify any consistent patterns to these behavioral changes. Nonetheless, one clear finding from these studies is that a prepulse inhibits the startle reflex on its initial presentation, even if, in so doing, it must overcome competing effects of reflex sensitization. The prepulse used in this study (5-ms duration, 16 dB over background) was not unusually intense compared with those used in many reports, and in previous reports comparable stimuli have been shown to not elicit a motor response in humans above that detected during the presentation of background noise (Swerdlow, Sprock, & Braff, 2006).

The finding that learning is not required for the expression of PPI does not preclude the possibility that PPI deficits in patient populations reflect learning deficits. To our knowledge, no published study has been designed to test this possibility. Based on the present findings, we reexamined data from the first prepulse + pulse trial presented to patients and normal comparison subjects (NCS) in our recent report of PPI deficits in schizophrenia (Swerdlow, Light, et al., 2006). Eighteen patients (10 men and 8 women) who were not taking atypical antipsychotics were matched by age and sex to 18 NCS. Percent PPI was compared between groups on the basis of the first prepulse + pulse trial (Trial 7, using a 15 dB over 70 dB(A) background 20-ms noise prepulse presented 30 ms prior to a 115 dB(A) 40-ms noise pulse) and the preceding startle pulse (Trial 6). Trials 1–5 contained only startle pulses. Despite the fact that a 30-ms prepulse interval produces submaximal PPI, mean %PPI among NCS was 37.70 ($SEM = 6.62$) and was significantly greater than zero ($p < .002$, sign test). In comparison, %PPI among patients ($M = -0.29$, $SEM = 19.54$), after excluding one subject whose startle amplitude on the pulse alone trial was 3.0 and whose %PPI was -1016.71), was not significantly different from zero, and differed from NCS by a large effect size ($d = 0.86$). Thus, although this retrospective analysis does not include balanced trial orders, it does confirm among NCS the present findings of PPI on the initial pairing of prepulse + pulse, and also suggests that PPI deficits in patients can be detected prior to any possible PPI “learning.”

In conclusion, robust acoustic PPI can occur on the first exposure to a discrete prepulse, and is thus not fully dependent on learning processes, using stimuli comparable to those that elicit PPI deficits in clinical populations. The present findings using discrete and relatively weak (above background) acoustic prepulses and a single prepulse interval build on earlier evidence that learning is not required for human PPI elicited with more intense prepulses and cross-modal PPI (Krauter et al., 1973). It is certainly possible that with repeated pairings of prepulses and pulses, learning might contribute to changes in PPI, and thereby account for either the increases or decreases in PPI that have variously been reported across the test session. Thus, the present evidence that PPI is not dependent on learning does not fully preclude the possible contribution of learning deficits to impaired PPI in clinical populations.

Acknowledgments

We acknowledge the expert technical assistance of Ashley Sutherland Owens, Sophia Lelham, Tijmen Schortinghuis, and Joyce Sprock, and the scientific input of Jim Ison. Maria Bongiovanni provided expert assistance in manuscript preparation. This research was supported by National Institute of Mental Health (NIMH) Grants MH59803 and MH69589. Neal R. Swerdlow has had grant support from Pfizer Pharmaceuticals and Allergan, Inc., and is a paid consultant to Sanofi/Aventis.

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Figure 1.

Schematic representation of the three configurations of two trials used in this study. In each configuration, the two trials were separated by 25 s. The control order ($n = 34$) consisted of two consecutive presentations of a 40-ms 118 dB(A) noise pulse (PA) superimposed on a 70 dB(A) background. In Order 1 ($n = 25$), PA was followed 25 s later by an identical pulse that was preceded 120 ms by a 5-ms noise prepulse 16 dB over background (pp + P). In Order 2 ($n = 23$), pp + P was followed 25 s later by a PA.

Figure 2.

Startle magnitude, peak latency, and onset latency for the control order. Compared with the first trial, startle in the second trial had significantly greater magnitude and shorter latencies.

Figure 3.

Startle magnitude and PPI in Order 1 and Order 2. A. Compared with the PA trial, startle magnitude on the pp + P trial was reduced significantly in Order 2 (#) but not in Order 1. Note that PA magnitude was greater in Order 2 versus Order 1 (*), consistent with the within-subject pattern detected in the control order (see Figure 2). B. Order 1 and 2 groups were balanced for startle magnitude on the PA trial by ranking subjects in each group according to mean PA magnitude and removing them sequentially until group means were identical. Even under conditions of identical PA magnitude, PPI was evident in Order 2 (#) but not Order 1. This is shown in Figure 4C (*), calculated as %PPI, and Figure 4D (*), calculated as a difference score. E. A “virtual” %PPI was calculated for the control order, treating Trial 1 as the PA and Trial 2 as the pp + P. This yielded significant prepulse potentiation (shown as a large negative value for %PPI); in comparison, %PPI in Order 1 was significantly greater (*). F. A “virtual” %PPI was calculated for the control order, treating Trial 2 as the PA and Trial 1 as the pp + P. In comparison to the “virtual” value for the control group, %PPI in Order 2 was significantly greater (*).

Figure 4.

Prepulse effects on peak and onset startle latencies in Order 1 and Order 2. A. Peak latency facilitation was evident in Order 1 but not Order 2. Note that PA latency was greater in Order 1 versus Order 2, consistent with the within-subject pattern detected in the control order (see Figure 2). B. Order 1 and 2 groups were balanced for peak latency on the PA trial by ranking subjects in each group according to mean PA peak latency and removing them sequentially until group means were identical. Even under conditions of identical PA peak latency, peak latency facilitation was evident in Order 2 but not Order 1. Identical patterns are evident for onset latency (Figure 4C and 4D).

Table 1

Subject Characteristics

Characteristic	Control (<i>n</i> = 34)	Order 1 (<i>n</i> = 25)	Order 2 (<i>n</i> = 23)
Gender (male:female), <i>n</i>	24:10	13:12	11:12
Mean (range) age (years)	23.3 (18–31)	24.6 (18–34)	22.9 (18–35)
Mean (range) education (years)	14.7 (12–20)	14.9 (12–18)	14.7 (12–20)
Ethnicity (C:A:AA:H:NR), <i>n</i>	11:12:3:7:1	7:10:4:3:1	9:8:3:3:0

Note. C = Caucasian; A = Asian; AA = African American; H = Hispanic; NR = not reported.